```
- - - - - - - - - - - - - - - - - - -x
                                     :
U.S. ENVIRONMENTAL                   :
                                     :
PROTECTION AGENCY                    :
                                     :
- - - - - - - - - - - - - - - - - - -x
```

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

CONSULTATION ON DERMAL SENSITIZATION

ISSUES FOR EXPOSURES TO PESTICIDES

May 4, 2004

[8:40 a.m.]

Holiday Inn Rosslyn at Key Bridge
1900 North Fort Myer Drive
Arlington, Virginia 22209

PARTICIPANTS

FIFRA SAP Session Chair

Steven Heeringa, Ph.D.

Designated Federal Official

Mr. Paul Lewis

FIFRA Scientific Advisory Panel Members

Stuart Handwerger, M.D.

Gary Isom, Ph.D.

Mary Anna Thrall, D.V.M.

FQPA Science Review Board Members

Paul Bailey, Ph.D.

Gary Burleson, Ph.D.

Ih Chu, Ph.D.

Iain Foulds, F.R.C.P.

A. Wallace Hayes, Ph.D., DABT, FATS, FIBiol., FACFE, ERT

Abigail Jacobs, Ph.D.

Jean Meade, D.V.M., Ph.D.

Torkil Menne, M.D.

Nancy Monteiro-Riviere, Ph.D., DABFE, DABFM

Richard Pleus, Ph.D.

Paul Siegel, Ph.D., MSPH

EPA OFFICIALS

Joseph J. Merenda, Jr. (OSCP)

Jim Jones (OPP)

Timothy McMahon, Ph.D. (OPP)

Jonathan Chen, Ph.D. (OPP)

P R O C E D I N G S

DR. HEERINGA: Good morning, everyone, and welcome to our two-day, three-day meeting of the FIFRA Scientific Advisory Panel, the topic being "Consultation on Dermal Sensitization Issues for Exposures to Pesticides."

I'm Steven Heeringa. And I'm a biostatistician from the University of Michigan Institute for Social Research. I'm a permanent member of the SAP Panel and will serve as the chairperson for the Panel for the next three days.

My responsibility is primarily to keep things moving here and to draw on the assembled expertise of the substantive topic Panel members.

Before we begin proceedings, I'd like to have everyone on the Panel introduce themselves, state their name, and provide their affiliation and their background. And

I'd like to begin here to my left with Stuart Handwerger.

DR. HANDWERGER: I'm Stuart Handwerger. I'm from the University of Cincinnati Children's Hospital Medical Center. I'm a pediatric endocrinologist. And my major research interest is in the hormonal control of human fetal growth and metabolism.

DR. THRALL: Good morning. I'm Mary Anna Thrall. I am a professor of pathology at Colorado State University.

DR. ISOM: I'm Gary Isom, professor of toxicology at Prudue University. And my area of interest is neural toxicology and specifically, mitochondrial toxins.

DR. PLEUS: Good morning. My name is Richard Pleus. I'm the director of Intertox, Seattle, Washington. My area of interest besides general toxicology is pharmacology, neurotoxicology, and developmental biology.

DR. HAYES: I'm Wally Hayes, Harvard School of Public Health. A toxicologist with an interest in risk assessment and alternatives.

DR. MENNE: I'm Torkil Menne from the University of Copenhagen. I'm a professor at the Department of Dermatology. My main research interest is in allergic contact dermatitis and particularly in nickel chromate and preservatives.

DR. FOULDS: I'm Iain Foulds. I'm a Consultant Dermatologist in Birmingham in the United Kingdom. I run a contact dermatitis clinic for occupational skin disease. And I have a research base at the Institute of Occupation Health at the University of the Birmingham.

DR. MONTEIRO-RIVIERE: I'm Nancy Monteiro-Riviere, North Carolina State University. I'm a professor of investigative dermatology and toxicology. My area of interest is dermatotoxicology.

DR. SIEGEL: My name is Paul Siegel. I'm with the National Institute for Occupational Safety and Health Effects Laboratory Division. I'm the team leader for bioorganic chemistry. My main research area of interest is hypersensitivity diseases.

DR. CHU: Good morning. I'm Ih Chu from Health Canada, a toxicologist. My research interest is in systemic effects and pharmacokinetics. Thank you.

DR. JACOBS: I'm Abby Jacobs from the Center of Drug Evaluation and Research, FDA. And I'm a toxicologist.

DR. BAILEY: My name is Paul Bailey. I'm a toxicologist with ExxonMobile. My research interests are in the areas of contact dermatitis and occupational dermatitis.

DR. MEADE: Good morning. I'm Jean Meade. I'm with the National Institute for Occupational Safety and Health. I'm in the agriculture and immunotoxicology group. I am team leader for the immunotox group.

DR. HEERINGA: Thank you very much.

At this point in allergic contact dermatitis, I'd like to introduce the designated Federal Official for this meeting, Mr. Paul Lewis. And Paul will have some comments on meeting procedures and protocol.

MR. LEWIS: Thank you, Dr. Heeringa. I'm Paul Lewis, and I'll be serving as the Designated Federal Official for this meeting of FIFRA Scientific Advisory Panel over the next three days. I'd like to thank Dr. Heeringa and members of the Panel of agreeing to serve for substantive discussions over the next three days and for Dr. Heeringa for serving as our Chair. We appreciate the allergic contact dermatitis and the effort of the Panel members in preparing for the meeting taking into account their busy schedules.

By way of background, the FIFRA SAP

is a Federal Advisory Committee and provides independent scientific peer review and advice to the Agency on pesticides and pesticide-related issues regarding the impact of proposed regulatory actions on human health in the environment. The FIFRA SAP only provides advice and recommendations to the Agency, while decision-making and implementation authority remains with the EPA.

FIFRA established what is called a permanent panel which consists of seven members. The expertise of the Panel is also augmented through a Science Review Board. And Science Review Board members would be these ad hoc members are temporary members of the FIFRA SAP, providing additional scientific expertise to assist in reviews conducted by the Panel.

As the Designated Federal Official for this meeting, I serve as a liaison between the Panel and the Agency. And I'm also responsible for ensuring that the provisions of the Federal Advisory Committee Act are met.

The Federal Advisory Committee Act of 1972 established a system of governing the creation, operation, and termination of executive branch advisory committees. FIFRA SAP is subject to all FACA requirements. These include having open meetings, such as we're having here today, timely public notice of all meetings, and document availability. And all documents are available -- I will discuss that a little bit later on -- through EPA Office of Pesticide Program's Public Docket.

As the Designated Federal Official for this meeting, a critical responsibility is to work with appropriate Agency officials to ensure all ethics regulations are satisfied. In that capacity, Panel members are briefed with the provisions of the Federal Conflict of Interest Laws. Each participant has filed a standard report government financial disclosure report.

I, along with our deputy ethics officer for the Office of Prevention of Pesticides and Toxic Substance, and in consultation with the office general counsel, have reviewed each report to ensure all ethics requirements are met. And a sample copy of this form is available on the FIFRA SAP web site.

The Panel will be reviewing several challenging issues over the next three days. We have a full agenda, and meeting times are approximate. Thus we may not keep to the exact times as noted due to Panel discussions and public comments. We strive to ensure adequate allergic contact dermatitis for Agency presentations, public comments to be presented, and Panel deliberations.

For presenters, Panel members, public commenters, please identify yourself and speak into the microphones since this meeting is being recorded.

Copies of presentation materials and public comments will be available in the EPA Office of Pesticide Programs docket in the next few days.

For members of the public requesting allergic contact dermatitis to make a public comment, please limit your comments to five minutes unless prior arrangements have been made. For those that have not preregistered, please notify myself or members of the FIFRA SAP support staff if you're interested in making a comment.

As I mentioned previously, there is a public document for this meeting. All background materials, questions posed to the Panel by the Agency, and other documents related to this SAP meeting are available in docket. Additional overhead slides presented will be available in the next few days.

In addition, the major substantive

background materials are also available on the web site. This includes the meeting agenda, listed Panel members, the background document, and the charge to the Panel.

For members of the press, Mr. Douglas Parsons, Director of Communications, Media Office of OPPS is available to answer your questions at this meeting. Mr. Parsons is standing right here. So we request all members of the public who have questions about the operations of this meeting or any press inquiries, please direct those questions to Mr. Parsons.

At the conclusion of this meeting, the SAP will prepare a report as response to questions posed by the Agency, background materials, presentations, and public comments. And this report serves as meeting minutes. We anticipate the meeting minutes will be completed in approximately six to eight weeks after this meeting and, again, will be available in the Office of Pesticide Programs docket in addition to being posted on our EPA FIFRA SAP web site.

I want to thank members of the public and, again, for Panel members for participating in today's meeting and over the next three days of discussion. I'm looking forward both to challenging, interesting discussions during the course of our meeting.

Thank you. Dr. Heeringa.

DR. HEERINGA: Thank you, Paul.

Just a few comments before we begin the formal session. I should point out that one of our Panel members, Dr. Gary Burleson, will be arriving this afternoon. So he is a member of the Panel, and we'll have him introduce himself at that point.

As the chairperson for this meeting, again, I indicated my role here is primarily to make sure that we get as open and accurate an exchange of information and views as we possibly can over the course of the next two to three days. I do want to emphasize, and I think all of us realize, that this is a Scientific Advisory Panel; and, therefore, we will focus our efforts on the science of the issues at hand related to dermal sensitization.

With regard to actual process, a minor detail but an important one as probably my major role as chair, that is to make sure that, if you use the microphone to make comments, state your name before you actually use the microphone. We are transcribing this onto audio tape, and it's important to identify yourself before you speak. That applies to Panel members and also to public commenters and other members of the audience who may be brought forward to provide specific information.

And, finally, with regard to the flow of materials, if this meeting progresses as many of the others that I've been involved in, there will be an exchange of materials that will take place, either in the form of copies of overheads of presentations, papers that are submitted for additional review or information. Please be sure that a copy of those materials is given to Mr. Lewis so that it can be included in the EPA docket and, therefore, be made available publicly. And it is the fact that if you provide something to the Panel, it will be part of the docket so it will become public.

So with those few administrative notes, I guess I would like to formally begin. And in doing so, I'd like to welcome Mr. Joseph Merenda, who is Director of the Office of Science Coordination and Policy for the EPA.

Good morning, Joe.

DR. MERENDA: Thank you, Dr. Heeringa. Good morning and welcome.

Taking the cue from Dr. Heeringa, my name is Joe Merenda for the U.S. Environmental Protection Agency. And it is my pleasure this morning to welcome Panel members and members of the public to the FIFRA Science Advisory Panel.

On behalf of EPA, let me express our great appreciation to all of you who have volunteered to serve on this Science Advisory Panel. The availability to EPA of independent external expert scientific advice is critical to our ability as an agency to meet our objectives of using high-quality science in making our programmatic and regulatory decisions. And it's also important for us to do so in a public and transparent manner. And that is the key things that these types of advisory committee meetings are all about, to bring key scientific issues out into the open and get the best advice that the Agency can as we move forward with our programs.

This is going to be a challenging set of issues. We never bring the easy ones to the FIFRA Science Advisory Panel. But I'm sure you are all up to that challenge. And I look forward to some very thorough and intensive discussions over the next couple of days.

Thank you and welcome.

DR. HEERINGA: Thank you, Mr. Merenda.

At this point in allergic contact dermatitis, I'd like to also introduce Mr. Jim Jones who is Director of the Office of Pesticide Programs at the EPA.

MS. JONES: Thank you, Dr. Heeringa. And I will also add to Joe's thanks to the permanent members of the SAP as well as the ad hoc members who are joining us over the next couple of days on these very challenging issues.

To reinforce what Dr. Heeringa said,

we have gathered all of you here over these couple of days to focus on the scientific issues that we're going to be putting before all of you as it relates to determine sensitization, in particular as it relates to determine sensitization to chromium.

I would like to give you a little bit of the context within which we're operating so you understand how the science that you're going to be discussing with us and amongst each other will ultimately fit into the regulatory decision-making issue that we have before all of us at the Agency right now.

Many of you may be aware that one of the principal, if not perhaps the principal, wood preservatives used for residential uses in the United States, referred to as CCA, was voluntarily canceled. That cancellation became effective December 31 of last year, 2003. There are a number of alternative products that are currently registered either copper-based or chromium-based products that are available for use. And the Agency has before it an application for registration of a product where its principal component is chromium and has a degree of chromium greater than we had seen in the CCA products. And we are in the process at the Agency of analyzing the risks and the benefits of this product that's before us.

The issues that we are talking about here today as it relates to the hazards associated with chromium, in particular as it relates potentially to determine sensitization, will ultimately that advice will be used by the Agency in finalizing our hazards characterization around chromium.

Of course, there are other hazards associated with chromium. Those are issues that we have veted with other SAPs and internally and feel pretty confident around our assessments there. There certainly are exposure issues. And we've been working to get a better understanding of the exposure issue with other parts of the Agency with the registrant of this product. And so I think that we have a general path forward on understanding the exposure issues associated with the product before us.

What we are talking with all of you about is this one aspect of the hazard of chromium. And it is after we get the advice of this Panel. And, again, we will come to our final conclusions as it relates to that part of the hazard. We will then take that information, along with other endpoints as it relates to chromium, the exposure as it relates to the proposed use in front of us; and we will ultimately make a decision.

In the licensing arena, that's the arena that we work in here in the pesticides program, we license pesticide products. A product cannot be used in the United States unless we license it for that use. We refer to that as "registration." There is no such thing as no decision. You either get a license or you don't. And if you don't get a license, you can't sell the product. If you do get a license, you can sell the product.

So we are faced with making a decision around this issue. And we will be making a decision in relatively short order. A decision that won't be made until after we have gotten the advice of this Panel and some additional information that we're working on as it relates to exposure; but a decision will be made by the Agency in the coming months.

So I just wanted to give you some sense of the degree to which the advice that you'll be providing to us, not only over the next two days but in the final report that we get from the Panel, how that will fit into a regulatory decision-making process within the Agency.

I look very much forward to the next couple of days. I think we'll have an interesting exchange and to the ultimate receipt of the report from this Panel.

Thank you.

DR. HEERINGA: Thank you very much, Mr. Jones, for providing that context. It's very, very useful.

At this point in allergic contact dermatitis, I think we're ready to begin our initial scientific presentations from the research staff of the Environmental Protection Agency. And the first scheduled presenter is Dr. Timothy McMahon, who is of the Office of Pesticide Programs. And he's going to be presenting on Proposed Hazard Identification Methodology for Assessment of Dermal Sensitization of Risk.

Dr. McMahon.

DR. MCMAHON: Thank you, Dr. Heeringa.

Good morning, Mr. Chairman, members of the Panel, ladies and gentlemen. I am Dr. Timothy F. McMahon, Senior Toxicologist in the Antimicrobials Division, Office of Pesticide Programs. I am here with my colleague Dr. Jonathan Chen of the Antimicrobials Division as well to present a set of issues related to proposed hazard identification methodology for quantification of dermal sensitization.

Specifically, the Agency is interested in developing the foundation of a scientifically sound approach to quantitative assessment of dermal sensitization to pesticide chemicals, including pesticide chemicals that are incorporated into other materials, that is, treated articles.

The information presented today is derived from several published articles in peer-reviewed scientific journals and books. Where appropriate, reference is also made to publicly available publications from the USEPA and state regulatory agency publications.

The outline of my presentation will be as follows: I will present the current regulatory approach in the Office of Pesticide Programs with regard to assessment of dermal sensitization and will then present a brief overview of the biology of dermal sensitization.

Following this, I will present methods currently proposed for estimation of safe area doses for protection against induction of sensitization and for protection against elicitation of sensitization reactions in sensitized individuals.

Areas of scientific uncertainty that need to be considered in such approaches will then be presented including available data on relative sensitivity of children vs. adults.

After my general presentation, hexavalent chromium as a case study will be presented by Dr. Chen, including the available hazard data that estimates safe area doses for protection against induction and elicitation of dermal sensitization to hexavalent chromium.

Before I begin, I would first like to acknowledge the assistance of several of my colleagues at USEPA, including from the Office of Pesticide Programs Norm Cook, Nader Elkassabany, Tim Leighton, Bill Jordan, and Winston Dang; from the Office of Research and Development, Denise Sailstad; from the Office of Solid Waste and Emergency Response, Michele Burgess and Lee Hoffman; from the Office of Science Coordination and Policy, Joseph Merenda, Jr., and Karen Hamerneck; and from the Office of Water, Nancy Chu.

Under the current regulatory approach in the Office of Pesticide Programs, 40 CFR 798.4100 states that: "Information derived from tests for skin sensitization serves to identify the possible hazard to a population repeatedly exposed to a test substance."

Hazard in this approach is defined by the results of the currently accepted dermal sensitization tests, which include the Buehler test, the maximization test, and, more recently, the murine Local Lymph Node Assay.

These tests serve to identify whether a pesticide chemical is capable of causing an allergic contact dermatitis in exposed experimental animals and primarily give a "yes/no" answer to the question although we will see later that the Local Lymph Node Assay has been proposed for additional uses in determination of dermal sensitization hazard.

Other government agencies have been found to use a similar approach under current regulatory schemes. The U.S. Food and Drug Administration under FFDCA Section 601 with respect to cosmetics prohibits distribution of cosmetics in interstate commerce which are adulterated or misbranded. A cosmetic is considered adulterated if it contains a substance which may makes the product harmful or injurious to consumers under customary conditions of use, including the potential for dermal sensitization. Under such circumstances, if tests are needed, classical animals tests or in vitro alternative tests are used.

With respect to topically applied drugs, the FDA, in published guidance, cites the Buehler and guinea pig maximization tests as reliable assays for determining sensitization potential; and the LLNA is cited as a quantitative rather than essentially subjective test.

The Consumer Products Safety Commission under 1500.3(b)(9), states that "Before designating any substance as a strong sensitizer, the Commission, upon consideration of the frequency of occurrence and severity of the reaction, shall find that the substance has a significant potential for causing hypersensitivity." To determine whether the substance is a "strong" sensitizer, the CPSC will include, among other factors, "the result of experimental assays in animals or humans, considering dose-response factors, with human data taking precedence over animal data."

With respect to pesticides, when a chemical is found to be a sensitizer using current testing methods, a qualitative assessment is performed. Occupational dermal exposures can be dealt with appropriately either through engineering controls or use of personal protective equipment. Non-occupational exposures can normally be dealt with through appropriate precautionary labeling statements.

It has become apparent in recent years, however, that this approach may not always be adequate. For the agricultural herbicide trifluralin, for example, dermal sensitization was recognized as an adverse effect for which the Health Effects Division's Hazard Identification Assessment Review Committee recommended that the Local Lymph Node Assay be used to define a NOAEL and allow quantification.

There also exists the manufacture of treated articles of substances in which a registered pesticide is incorporated into the article to protect the integrity of the article of substance itself such as paint treated with a pesticide to protect the paint coating or wood products treated to protect the wood against fungal or insect decay.

Under such circumstances of use, the general public may unknowingly be exposed to pesticide chemical in the treated article. Therefore, prior to such use, the pesticide chemical must be registered under FIFRA, which requires that the manufacturer of the pesticide demonstrate that it can be used without unreasonable risks to humans or the environment.

Treated articles such as preserved wood however, do not bear a pesticide label or effectively use other communication methods to inform and protect people against potential hazards, including the potential for dermal sensitization.

This brings us to the purpose of today's consultation. EPA's Office of Pesticides Programs is seeking expert advice on how to evaluate general population exposure to a pesticide that is recognized to cause dermal sensitization. Specifically, the Agency is interested in better understanding how such exposures may induce sensitization in the general population and how to establish criteria to protect against unacceptable dermal reaction. The Agency is also seeking guidance from the SAP on how such exposures impact individuals already sensitized.

A brief overview of allergic contact dermatitis -- this is also known as contact hypersensitivity, contact allergy, or delayed contact hypersensitivity -- has been defined by Marzulli and Maibach as "a delayed, immunologically mediated, inflammatory skin disease consisting of various degrees of erythema, edema, and vesiculation."

Kimber has also defined sensitization as "stimulation by chemical allergen in an inherently susceptible individual of an immune response of the quality and vigor required to permit the provocation of an elicitation reaction upon subsequent encounter with the same chemical."

Allergic Contact Dermatitis is usually characterized by two phases which we term induction and elicitation or challenge.

Induction is defined as an exposure

of sufficient magnitude and or duration to activate a specific immune mechanism resulting the acquisition of sensitization, whereas elicitation or challenge is defined as responses in dose to the sensitized individuals upon exposure to the allergen by a relevant route.

When we compare dermal irritation with sensitization, we see two main important differences, primarily the delayed nature of the response in allergic contact dermatitis as the requirement for immune memory.

To be capable of inducing an allergenic response, the chemical itself must possess certain characteristics. Those chemicals able to cause sensitization are usually low molecular weight protein-reactive substances that can gain access to the viable epidermis via the stratum corneum, and are also able to cause sufficient local trauma to induce cutaneous cytokines and be inherently antigenic and recognized by responsive T lymphocytes.

This schematic shows you the basic biology of contact hypersensitivy. On the left, illustrating induction phase. Once through the stratum corneum, the allergen makes contact with the Langerhans cell, a member of the bone-marrow derived dendritic cell family whose function is to act as a sentinel cell and serve as a trap for antigens entering the skin.

Langerhans cells then direct the allergen to a regional lymph node, where interaction with T lymphocytes occurs, followed by proliferation of lymphocytes that have been primed to react against the presented antigen.

A subsequent contact with the allergen as shown on the right will result in elicitation of the sensitization response due to the reaction of sensitized lymphocytes with the allergen.

It is worth mentioning here that, in addition to Langerhans cells, epidermal cytokines and chemokines may also play a role in the development of the sensitization response. This is based on the observation that the functional activity of Langerhans cells, and presumably other cutaneous antigen-presenting cells, is regulated largely by the availability of cytokines.

Although allergic contact has been characterized as a threshold type of response, that is, below a certain concentration that would not be expected to occur, thresholds are largely determined by the potency of the allergen, and induction/elicitation thresholds vary among individuals.

Dose-response relationships are also observed for both the induction and elicitation phases and thresholds for induction can be reached following either a single sufficiently high amount of exposure to the allergenic chemical, or after contact with large areas of skin, or as a consequence of repeated skin applications.

In some cases, such as with the sensitizer 2,4-dinitrochlorobenzene, a single contact can be sufficient for sensitization; and some data suggest that sensitizing potential may increase with repeated exposures.

I would like to present an overview of methods for hazard assessment of dermal sensitization.

The classical animal tests for dermal sensitization that have found wide use are the maximization test and the Buehler test, both usually performed using guinea pigs. This slide illustrates the basic study design of each type of assay.

The guinea pig maximization test uses intradermal injection with and without

FCA for induction followed on days 5 to 8 by topical induction/irritation, followed again by topical challenge on days 20 to 22. Readings are made at 24 hours after the challenge dose and then again at 48 hours.

The Buehler test uses topical administration via closed patch on the shaved flank for induction on days 0, 6 to 8, and 13 to 15. Challenge is made on the untreated flank for 6 hours on day 27 to 28 and readings made at 24 and 48 hours post-challenge.

The Buehler test and the maximization test are best suited for providing a yes/no answer to whether a substance is a sensitizer or not. The local lymph node assay is a more recent test method for assessing the allergic contact dermatitis potential of chemicals, specifically the induction phase of sensitization.

The LLNA measures the incorporation of H-methylthymidine or iododeoxyuridine into proliferating lymphocytes in the draining auricular lymph nodes of mice following the topical application of the chemical as shown. The assay compares the mean disintegrations per minute from the test group to the control group to give a stimulation index or SI.

From the data, it is possible to estimate the concentration of test chemical required to give an SI of 3. This estimated concentration is known as the EC3 value. An SI of 3 or greater is considered evidence in this assay that the chemical is a sensitizer.

As an alternative to the traditional testing that LLNA provides potential for determining NOAEL, the use of fewer animals, the evaluation of induction phase provides a biological basis for the endpoint of concern. And now it also provides extensive assay data available for the test.

In 1999, the Interagency Coordinating Committee on the Validation of

Alternative Methods Immunotoxicity Working Group recommended the LLNA as a stand-alone alternative for contact sensitization hazard assessment provided that certain protocol modifications were made. At that time, the ICCVAM IWG considered that the LLNA was not appropriate for certain classes of chemicals, including metals, strong irritants, and aqueous soluble materials.

Following additional studies, the FIFRA SAP in 2001 agreed with the Agency proposal that the LLNA was applicable for testing chemicals to elicit contact sensitization and should be considered a preferred, stand-along assay. The SAP also notes that expanding application of the LLNA to metals, strong irritants, and aqueous soluble material should be considered based on additional evidence published since the 1999 ICCVAM peer review.

Now I'd like to talk a little bit

about methods for determination for induction thresholds.

Approaches for determination of quantitative assessment of sensitization induction thresholds have been published, proposed in the scientific literature using LLNA data like Gerberick and Griem. As reviewed by Felter in 2003 and Gerberick in 2001 proposed a methodology for determination of a sensitization reference dose for sensitizers in consumer products.

This method employs the same fundamental concepts of a risk assessment including hazard identification, dose response assessment, exposure assessment, and risk characterization. Hazard is first identified performed using results of laboratory animal tests such as the LLNA, structure-activity relationships, or the results of human experience.

Once the hazard is adequately

identified, a dose-response assessment is performed using a weight-of-evidence approach in which chemicals are categorized into potency classes. Specific NOAEL values are not applied in this paradigm, as data are not always sufficiently robust to identify a NOAEL with a high degree of confidence, thus the use of potency categories shown in the next slide.

For each potency category, a default NOAEL, as shown on the right, is assigned. The lower boundary of the potency category for a sensitizing chemical is then used as the starting point.

The application of uncertainty factors is then applied to account for intraspecies variation vehicle product matrix effects and exposure considerations. A maximum uncertainty factor for each area is 10 of the maximum total uncertainty of 1000.

Calculation of a Sensitization Reference Dose is then made with comparison to exposure estimates to determine a margin of safety. This approach has been applied to consumer products containing fragrance chemicals that have contact sensitization potential for determination of safe levels in the product.

Although the approach assesses the hazard of induction of allergic contact dermatitis, the same approach is proposed for application to elicitation if the threshold for elicitation is known or a factor for converting an indication threshold to an elicitation threshold is used. We will see later that Griem et al. have employed a similar concept for calculation of safe area doses for elicitation thresholds.

In 2003, Griem published a paper proposing an approach of deriving a safe area dose skin dose for induction based on the use of LLNA data. He made a comparison between EC3 values from LLNA tests with NOAEL or LOAEL values from human repeat insult patch tests or human maximization tests for approximately 30 known human chemical sensitizers.

Comparison of the molar area doses causing induction showed a good correlation; therefore, it was proposed that the EC3 values could be used as a surrogate for human NOAEL values and thus as a starting point in quantitative risk assessment.

As shown here from the published paper, comparison of molar area doses between LLNA tests and human test results showed a fairly good correlation. And as I said, therefore, the EC3 values were proposed as surrogate values for use as a starting point in the risk assessment.

Uncertainty factors were then applied for interspecies extrapolation, intraspecies variation, and to account for possible higher inducing potency of a chemical upon repeated exposure. The LLNA EC3 value was then divided by the total uncertainty factor of 300 to obtain a safe area dose which should not induce sensitization the vast majority of humans.

Combined with a reasonable exposure assessment, the concept was proposed to lead to derivation of acceptable concentrations for sensitizing chemicals in the workplace, in cosmetics, and in household products.

And now I'd like to go through some proposed methods for determination of elicitation thresholds. Methods have also been proposed for determination of concentrations or safe area doses for protection against elicitation in sensitized individuals. By inference, protection against elicitation would also be protective of induction as thresholds for induction are generally higher than those for elicitation.

Griem in the same publication in 2003 proposed an approach for estimation of safe area doses for elicitation on the assumption that a correlation between the induction potency and elicitation potency of a chemical could be established. As several of the factors that influence induction of sensitization, such as skin penetration, uptake by antigen-presenting cells, and metabolism, are also relevant for elicitation.

However, a comparison of induction and elicitation area doses from limited data in humans showed that while induction threshold doses spanned five orders of magnitude, values for elicitation were mainly within one order of magnitude. I'm showing the poor correlation obtained there on this slide from his publication.

So, therefore, relevance for assessing the elicitation was the ratio of induction to elicitation threshold a linear correlation was described to relationship between the log transformation of the induction elicitation threshold ratio and the log transformation threshold.

Based on this using it was proposed that the induction elicitation threshold ratio can be predicted on the basis of an established induction threshold. And showing the log transformation of that linear correlation here with the equation describing that relationship.

So when based on this publication and based on the EC3 induction threshold from the local lymph node assay, a total uncertainty factor of 300 was proposed, a 3x for inter species, a 10x for intraspecies, and a 10x for repeated exposures. And the proposal was based on a NOAEL or LOAEL from the one-time human patch test or sensitization potency from the local lymph node assay a total uncertainty factor could range from 100 to 1000 plus the inclusion of a variable uncertainty factor based on the linear correlation as shown on the previous slide.

As one example from Griem's public comment for the EC3 value that he wrote of 8.8 microgram per square centimeter he applied uncertainty factors of 1x for interspecies, 10x for intraspecies, 10x for repeated exposure and 15x induction elicitation factor of a total uncertainty factor of 1500 for determination of a safe area dose of 0.006 micrograms per square centimeter.

Similarly, from a benchmark value of 0.05 microgram per square centimeter from human data, uncertainty factors were applied for interspecies 10x, 3x for repeated exposure for a total uncertainty factor of 30 in the derivation of a safe area dose is 0.002 micrograms per square centimeter.

An additional proposed approach for determination of safe area doses for elicitation is the concept of the Minimum Elicitation Threshold or MET. This is based on the notion that there is an elicitation threshold below which no sensitization reaction is expected.

The estimation of a MET is usually based on the results of tests in previously sensitized individuals; thus, it is considered protective of elicitation reactions. However, there has not been an extensive discussion of the criteria for employing this concept for purposes of risk assessment.

It is not certain what level of elicitation in a study population constitutes a valid hazard criterion. Moreover, it is not certain that the MET can be applied to all sensitizers.

I'd like to now go through a brief discussion of some of the uncertainty factors that are applied in these proposed approaches. Areas of uncertainty include interspecies, intra-species variations, product matrix effects; and exposure considerations such as area of the body exposed and repeated exposures.

For interspecies extrapolation this uncertainty factor is intended to account for differences in response from animals to humans. As reported by Griem, in sensitizing area, doses are similar for murine LLNA in human data; therefore, the interspecies factor in his proposal may be less than 10. But not all proposals use this factor.

Felter recognized this factor but also recognizes that the murine LLNA has not been yet used for derivation for a NOAEL for use in quantitative assessment and therefore relies on a default categories as a conservative approach. Intra-species variation is a 10x factor based on age, sex, and genetic makeup.

For product matrix effects, a range of 1 to 10 is proposed to account for the exposure to the contact allergen in the product matrix vs. results from experimental studies which typically is simple vehicles as various components of the product may effect a sensitizing potency of the allergen. But smaller factors may also be considered for mild formulations.

With respect to exposure variables, a proposed factor ranging from 1 to 10x was proposed to account for things such as site of body exposed, the effects of occlusion, and environmental conditions such as temperature, humidity, and repeated exposures.

Consideration should be given to whether there are potentially susceptible subpopulations who may be more susceptible to the induction and/or elicitation of allergic contact dermatitis. In addition, children's susceptibility also needs to be considered in determining populations potentially at risk.

Paustenback addressed the issue specifically for hexavalent chromium, and concluded that risk to children ages 3 to 8 is not likely to be greater than risk to adults as there is no evidence that repeated exposures to hexavalent chromium places a person at greater risk of sensitization.

Felter suggested that infants and children may actually be at lower risk for development of allergic contact dermatitis based on data gathered from dinitrochlorobenzene, a poison ivy allergen, which showed less susceptibility to induction in infants and children compared to adults.

In contrast, a publication by Wohrl et al. in 2003 compiled patch test results in 2,766 patients suspected of contact allergy carried out over approximately 4 years at an allergy clinic in Vienna, Austria. Of 79 children aged 1 to 10 years that were part of this compilation, the general elicitation rate shown here showed the highest percentage response in the 1 to 10 year old age group with an age-related decline.

However, the elicitation rate for some contact sensitizers, as shown in the next slide, such as hexavalent chromium showed no significant difference in percentage response with age.

This concludes my general presentation. Thank you.

DR. HEERINGA: Thank you very much, Dr. McMahon.

At this point before we move on to Dr. Chen's, I would like to give the members of the panel a chance to ask questions of clarification or information of Dr. McMahon.

Are there any questions based on this presentation?

Very well. Everything was quite clear. One more time.

We're a little ahead of schedule, but I think we can move on to the next presentation. And I'd like to introduce at this point Dr. Jonathan Chen of the Office of Pesticide Programs. And he's going to be dealing specifically with the case study of Cr(VI) in Wood Preservatives.

DR. CHEN: Thank you.

Mr. Chairman, Honorable Panel members, Ladies and Gentlemen, my name is Jonathan Chen. And I am a toxicologist with the Antimicrobials Division in the Office of Pesticide Programs.

In the following section, we are going to use chromium wood preservatives as a case study to address the proposed Hazard Assessment for Dermal Sensitization.

Before we discuss the hazard assessment issue, I would like to review some general properties of chromium.

Chromium is present in the environment in several different forms. The most common forms are chromium, trivalent or Cr(III), and hexavent or Cr(IV).

Cr(III) occurs naturally in the environment and is an essential nutrient required by the human body to promote the action of insulin in body tissues so that sugar, protein, and fat can be used by the body. Cr(VI) and Cr(0) are generally produced by industrial processes.

The trivalent chromium compounds are generally insoluble in water. In contrast, most Cr(VI) compounds are readily soluble in water. The hexavalent chromium compounds are reduced to the trivalent form in the presence of oxidizable organic matter.

Cr(VI) is used as a component of wood preservatives. For example, CCA and ACC. CCA, the chromated copper arsenate wood preservative, contains chromium, copper, and arsenic as pesticidal compounds to protect wood from deterioration.

There are three formulations of CCA, each containing varying ratios of arsenic pentoxide, chromic acid, and cupric oxide.

CCA-type C was the most commonly used formulation for pressure treating lumber for residential applications.

ACC, acid copper chromate, is a liquid formulation that contains 50% active ingredients including copper and chromium and 50% dilutents such as water. ACC is another chromated wood preservative.

In the wood industry, the chromated wood preservatives are used to treat wood with high pressure. The wood preservatives are pressed into the space between wood fibers. Once being pressure-treated into wood, ACC would contain 50% more chromium compared with the wood treated with CCA-type C solution.

In the treatment process, the chromium will penetrate into the wood and become bound or fixed in the wood. The term fixation refers to the series of chemical reactions that take place after the wood has been pressure-treated. The primary reaction is to turn Cr(VI) into Cr(III) and bind to wood fiber and other ingredients including copper and/or arsenic.

There are many factors that can affect the degree of fixation. For example, the condition time, the temperature, the moisture content of the wood, the concentration of the wood preservatives, the type of wood, etc. Among all these parameters, temperature is considered as one of the most important factors. CCA fixation is a highly temperature-dependent event. Many investigators have demonstrated that fixation can be accelerated at higher ambient temperature.

For CCA, research indicates that fixation may range from more than 6 months at 4 degree C to about one hour at 90 degree C. In general, when the wood was kept at a freezing temperature, the fixation step will stop.

The concentration of reactants is also important. When the concentration of the reactants increase, the fixation time will increase. Therefore, ACC would take more time than CCA to fix into the pressure-treated wood.

Why fixation is important. Research indicates that Cr(VI) may leach to wood surface when the fixation process is complete.

Cr(VI) is considered one of the most common and potent contact sensitizers. Exposure occurs in a number of occupational settings, and nonoccupational exposures also occur.

In the year 2001, the OPP Hazard Identification Assessment Review Committee, (HIARC), evaluated the Cr(VI) database and concluded that: "The potent skin allergenicity of chromium has been well documented in the literature, and chromium compounds have been reported to be the most frequent sensitizing agent in man.

Most of the occurrences of contact dermatitis cited are the result of occupational exposures. For previously sensitized individuals, very low dosage of Cr(VI) can elicit allergic contact dermatitis. No end point will be selected for risk assessment. The risk concern of the dermal contact of Cr(VI) should be addressed through warning language used on the labels."

However, OPP's current concern is that for pesticide chemicals that are in consumer products, some of which are treated articles without a chance to include label warnings.

Therefore, the issue has been discussed in the 2001 SAP meeting held for "Preliminary Evaluation Of The Non-Dietary Hazard And Exposure to Children From Contact With Chromated Copper Arsenate Treated Wood

Playground Structures And Contaminated Soil."

"The Panel advised that EPA should base risk assessments for noncancer health effects of dermal exposure to hexavalent chromium on direct dermal effects, irritant, and allergic contact dermatitis. The Panel was unable to provide EPA with methods for establishing endpoints and determining dose response relationships for these effects."

This is the reason the Agency is using the Cr(VI) in the wood preservative as the case study for the quantitative risk assessment for dermal sensitization.

Before we discuss the issue, I would like to mention the term CCDS. CCDS stands for the Concentration of Concern for Dermal Sensitization. In other words, the Agency would consider that, when the concentration of the chemical causing dermal sensitization is below the CCDS, it is not likely to start the dermal sensitization reaction toward the concerned population.

There are two types of CCDS we need to be concerned about for allergic contact dermatitis issue. The first one is CCDS for induction phase, and the second one is CCDS for the elicitation phase.

Murine LLNA data were proposed to determine the CCDS for the induction phase of allergic contact dermatitis. The LLNA data (EC3 values) for hexavalent chromium using potassium dichromate as the test substances from five different laboratories were reported by Kimber et al. in 1995.

There are two different proposed approaches to establish the appropriate concentration for Dermal Sensitization CCDS. the first one is Griem et al. (2003) methods, and the second one is Gerberick et al. proposed in the 2000, 2001.

Let us discuss the Griem et al. approach first. According to Griem et al.

2003, when risk assessment is based on the EC3 LLNA value, a factor of 3 is proposed as interspecies uncertainty factor to account for experimental variability. In general, a factor of 10 is suggested to account for intraspecies variation.

There is another safety factor that has been proposed by Griem et al. in the year 2003. Dermal sensitization in many cases may need more than one exposure to start the reaction. To address the concern, a safety factor of 10 has been suggested. The proposed repeated exposure uncertainty factor would be 10.

Respectively for the five studies with an average CCDS based on the U.S. Laboratories data would be 0.038 ug/cm^2 and the general CCDS for induction phase for Cr(VI) would be 0.034 ug/cm^2 based on the Griem's approach.

Now, let's discuss Gerberick's

approach. Gerberick et al. in the year 2000, 2001, proposed a methodology for determination of a sensitization reference dose for sensitizers in consumer products. The lower boundary of other potency category for a sensitizing chemical is used as the No Observable Adverse Effect Level, NOAEL.

For example, if the LLNA EC3 value is greater than 10,000 (ug/Cm$^{2)}$, then this chemical is classified as an extremely weak dermal sensitizer and would use 10,000 ug/Cm^2 as the default NOAEL in the hazard assessment process.

For a chemical a causing LLNA EC3 value of 69 ug/Cm^2, the 69 ug/Cm^2 would locate between the range of 10-1,000 category; therefore, it is considered as a strong dermal sensitizer. It would use 10 ug/Cm^2 as the default NOAEL in the hazard assessment.

Therefore, the NOAEL defined for the five LLNA studies are determined to be 1, 10, 10, 10, and 10 ug/Cm^2 based on the Gerberick's approach.

Gerberick set the maximum uncertainty factor as 1000. For dermal sensitization according to Gerberick, there is no great differences between the mouse and the human data. Therefore, an interspecies uncertainty factor of 1 is proposed. An uncertainty factor of 10 is suggested to account for intraspecies variation.

Because the Cr(VI) leaches to the wood surface, it would be in the liquid state and direct dermal contact would be the primary concern. Therefore, a matrix uncertainty factor of 10 is set for this purpose.

An exposure consideration uncertainty factor of 10 was used to cover the potential differences in site of the body exposed, the integrity of the skin, potential for mucosal contact, occlusion, and environmental conditions. Based on this, the average CCDS for the induction phase is 0.01 based on Gerberick's approach.

Let us discuss the CCDS for elicitation phase. Calculations of CCDS for the elicitation phase were performed using both human study data and murine LLNA data.

There are three human studies that are considered for the determination of the CCDS for the elicitation phase: The Nethercott study in 1994; Hansen et al. in 2003, and Basketter et al. in 2001.

In the Nethercott 1994 study, 100 possible volunteers selected from examination of 6000 patient files from dermatologists. Eventually, 102 took part in the study. All were believed to be Cr(VI) sensitized based on previous patch tests performed by their physicians.

There are three rounds of testing included in the study. In Round 1, patch test with 4.4. ug of Cr (VI)/cm^2 to verify sensitization. Those responding positively moved on to the Round 2.

In the Round 2, patch testing with 0.108 and 0.088 ug/Cr(VI)/cm^2 and full concentrations of Cr(III). Those showing positive responses to the Cr(VI) were not tested in Round 3. Only those that did not respond were moved on to the Round 3.

In the Round 3, the negative responders in Round 2 were tested with Cr(VI) concentrations of 0.18 and 0.88 ug/cm^2.

In the study, the patch test results indicates there is one volunteer showing positive response at the lowest tested concentration 0.019 ug/cm^2. There are four volunteers showing positive response at 0.088 ug/cm^2. The cumulative response would be 9% positive response at 0.08 ug/cm^2.

Therefore, from this study, a 10% minimum elicitation threshold of 0.089 ug/cm^2 was reported. However, the lowest dose tested, 0.018 ug/cm^2, also showed a response.

Now let us take a look at the Hansen et al. 2003 study. The purpose of the study is to compare the 10% MET values for Cr(III) and Cr(VI) in the Cr(VI) sensitive patients.

In the study, 18 volunteers confirmed to be Cr(VI) sensitized, patch testing with a Finn Chambers with serial dilutions of Cr(VI) and Cr(III). There are around 20 patches tested at the same time.

Using a dose-response curve, the 10% MET for Cr(VI) was determined to be 0.03 ug/cm^2 that equals 1 ppm). The 10% MET for Cr(III) was determined to be 0.18 ug/cm^2. That is around 6 ppm. Both Cr(III) and Cr(VI) were capable of eliciting a response at low levels.

The third study we are going to discuss is the study done by Basketter et al. in (2001. The purpose of this study is to investigate the dose-response relationships for Cr(VI) elicitation in sensitized persons using both occluded patch and open application techniques.

There are 17 volunteers with a history of contact allergy to chromium included in this study. In Part I of the study, Finn Chambers applied for 2 days on the back with aqueous dilutions of potassium dichromate, 1, 10, 100, 1000 ppm, applied to normal skin and also to sites pre-treated with 0.2% sodium lauryl sulfate (SLS).

In Part II of the study, repeat open application tests (ROAT) conducted on some volunteers using the aqueous solutions of potassium dichromate containing 0.1% SLS. Initial concentrations of 5 and 10 ppm used; if negative, then 20 and 50 ppm used after a one-month rest period.

The results of the closed patch test, the normal skin, there were no reactions. In the SLS treatment, 2 out of 17 responded at 1 ppm. For the repeated open application test (ROAT), 3 out of 15 showed response at 5 and 10 ppm.

To calculate the CCDS for elicitation phase based on human data, OPP considered the Nethercott et al. 1994 is a well-controlled study and should be used for CCDS calculation.

Based on Nethercott's 1994 data, because at the lowest tested concentration 0.018 ug/cm^2, still one volunteer showed positive response; therefore, 0.018 ug/cm^2 was considered as the LOAEL, the lowest observable adverse effects levels. Because the data are from human studies, the interspecies extrapolation factor could be reduced to 1.

An intraspecies uncertainty factor of 3 is proposed based on the use of sensitized persons as elicitation thresholds have been found to be less variable than induction thresholds. An uncertainty factor of 3 is also applied for the use of LOAEL values as the studies were not designed for specific determination of a NOAEL. An uncertainty factor of 1 is proposed for exposure considerations based on the use of a sensitized study group.

The total uncertainty factor of 10 of 3 times 3 was applied to the reported human LOAEL values of 0.018 ug/cm^2, and the CCDS for the elicitation phase was determined as 0.0018 ug/cm^2.

If you use the 10% MET value as the LOAEL, the calculated CCDS for elicitation phase would be 0.0089 ug/cm^2.

A similar approach can be applied to the MET values from Hansen et al. in 2003 and Basketter et al. in 2001 studies. The calculated CCDS for elicitation phase would be 0.001 and 0.003 ug/cm^2 for persons previously sensitized to hexavalent chromium. These values are similar to the proposed value of

0.0018 ug/cm^2.

To calculate the CCDS for the elicitation phase using murine LLNA data has also been proposed by Griem et al. based on their 2003 publication and the public comments.

By using Griem's public comments approach, when the risk assessment is based on an EC3 LLNA value reported in Kimber et al. in 1995. Since the lower boundary for the EC3 range form several studies was used and the mouse seem to be at least as susceptible than human, an intraspecies uncertainty factor of 1 is considered to be adequate.

Since all human subpopulation can come into contact with chromium-treated wood and since contact of inflamed eczematous, hydrated or otherwise compromised skin cannot be excluded, an intraspecies uncertainty factor of 10 is considered adequate.

Since repeated daily exposure with

treated wood can be considered likely, and the half-life time of chromium in the skin is rather long, an uncertainty factor of time of 10 is proposed besides an uncertainty factor to account for the difference between the induction and elicitation of 15 included.

CCDS brings on the Kimber et al. for elicitation phase is .007 microgram per square centimeter.

The summary. Cr(VI) is a potent dermal sensitizer. It is able to induce and to elicit allergic contact dermatitis. Cr(III) is also capable of eliciting allergic contact dermatitis, but studies indicate that it is less potent than Cr(VI).

Using the LLNA data, two different approaches have been proposed to estimate the CCDS for the induction phase of dermal sensitization.

CCDS for Induction Phase proposed average induction CCDS for Cr(VI) is 0.034

ug/cm^2 based on the Griem approach is 0.01 ug/cm^2 based on the Gerberick approach.

CCDS for the elicitation phase based on the human data, Nethercott et al. in 1994 proposed Cr(VI) CCDS for the elicitation phase is 0.0018 ug/cm^2 based on the LOAEL and 0.0089 ug/cm^2 based on MET 10%.

Based on the LLNA data and using the Griem's approach, proposed average Cr(VI) CCDS for the elicitation phase is 0.007 ug/cm^2 based on the Kimber, et al., five studies.

That's the end of my presentation.

DR. HEERINGA: Thank you very much, Dr. Chen.

At this point, I'd like to ask the Panel if they have any questions for Dr. Chen on his presentation or the results of the research, the analysis of the research, that he has presented here or for Dr. McMahon as well if you had something. Yes. Dr. Menne.

DR. MENNE: I'd like to ask if there

was any quantitative data on the amount of hexavalent chromate leaching out chromate preserved wood. Is there any data on dust on the surfaces?

DR. CHEN: This is a very, very important question, actually. At this moment for CCA, we do have some hand-wipe data. But for ACC, it is one we don't. And for that reason, we like to have some kind of study that can show what will be the appropriate allergic contact dermatitis, what kind of temperature before the fixation is really complete. Because before that, Cr(VI) is likely to stay on the surface.

So at this moment, we don't have this kind of data for ACC.

MR. JONES: Although we are in the process of collecting data that indicate that. And in the next couple of months, I think we'll have a fairly robust data set that will give us a sense of how much of the chromium is wiped off on hands.

DR. HEERINGA: That was Mr. Jim Jones. Yes, Dr. Hayes.

DR. HAYES: Is there any information besides the Hansen study that Cr(III) is an sensitizer?

DR. CHEN: The Hansen study basically it demonstrates -- it's Cr(III) is an elicitation phase. It can induce that kind of reaction. And actually in the Nethercott study, they have also done the Cr(III) study. And it seems like there is no really positive response.

DR. HAYES: It was negative in that one. But Hansen is the only one where there is a positive response.

DR. CHEN: Yeah. But there's one thing that the Hansen study basically they are putting -- let's see -- around 20 different patches on the same individual and these kind of things. So in general, Cr(III) is considered -- it can become an inducer for the elicitation phase. But the difficulty is that, because it's Cr(III), it's very difficult to penetrate the skin. So if there are any kind of mechanics that can make the Cr(III) to penetrate skin, then it can induce elicitation of the allergenicity.

DR. HAYES: A second question: What's the basis for the number of significant figures that you're giving for all these METs and all the various numbers. You're carrying out to a large number of significant figures.

DR. CHEN: Well, at this moment, let's see, all these are with a different kind of approach -- no. Because we do have all these studies, it's a different kind of approaches. We are trying to demonstrate, you know, if we use this kind of approach, what kind of endpoint or CCDS would come out.

So at this moment, I think this is the major question that we'd like to ask the

Panel to help us to find out the best way to come out with the appropriate CCDS. So this is, I think, the important questions.

DR. HAYES: Thank you.

DR. HEERINGA: Dr. Menne.

DR. MENNE: It says there are some publications from the past concerning Cr(III) sensitivity and you say it's usually quite high concentrations. We in Europe in recent years have revisited this area because we're seeing quite a high number of acute dermatitis based on chromate. And that was one of the reasons, one of the background from this Hansen study. And to our surprise on this study, we actually saw some reactions to the trivalent chromate.

And one of the explanation, the difference from earlier studies, is that we used another scale of reading compared to former times. So that has explained a good deal of the differences, I think. And our argument for doing so is that, when we're using the agreed ICCD scale, it's in the diagnostic patch test. That's to say you need to have very stringent criteria when it is on the basis of a diagnoses with infiltration, wetness, and so on. And they need to be homogeneous.

But when you're making a threshold definition, it's not probably the best way to use this definition because, when you go down the threshold, you actually have concentrations which are not irritant in any controls. And that's to say any difference in the change from normal skin, that might be papules in the test area or redness, might be an indication of a start of a reaction. And then it's only a matter of allergic contact dermatitis that you have a full-blown reaction.

So that's just to explain that you have another threshold in this study. And that is because we are thinking that your philosophy that demanding the ICC criteria for the threshold maybe is not completely fair.

DR. HEERINGA: Thank you, Dr. Menne. Yes, Dr. Isom.

DR. ISOM: Is there any evidence for cross sensitivity between Cr(III) and Cr(VI). And if so, then would that produce effects in combined exposures have any implications?

DR. CHEN: Well, actually, the Hansen study would be a very good study because they did kind of combined, bring to the testing solutions. And because Cr(IV) is an irritant at a higher concentration. So like I mentioned earlier, if any condition that can help the Cr(III) to penetrate into the skin, then it can help it come up some correction. Is that right?

DR. MENNE: Yes. What we did in this study was that we actually also tested isolated with Cr(III), Cr(VI). And then you named a combination of the two -- and we didn't see any additive arsenatistic effect by the combination. And, of course, you can speculate a lot why this is. And we even speculated that the population, at least in a large part of Europe, is more exposed to Cr(III) than to hexavalent chromate and maybe it might play a role where you're primarily sensitized to Cr(III) and not hexavalent chromate. So we didn't see any additive affects. And we think that trivalent chromate might be a primary sensitizer, at least when it comes to acute dermatitis.

DR. HEERINGA: Thank you. Any other questions?

I have one for Dr. Chen. And it's just a point of information. Slide 7, you present a table which shows the composition of the CCA formulations and ACC. My recall is that it's CCA that is primarily used in residential applications for pressure-treated wood, and B and C are marine and industrial.

DR. CHEN: Well, Type C solution is a primary solution used for the residential.

DR. HEERINGA: Thank you. That's a correction. I'm sorry. Thank you.

Any other questions from the Panel?

At this point in allergic contact dermatitis, I have 10:06; and I think we're scheduled for a break. And so I would like to take a -- let's take a 15-minute break and actually reconvene here at 10:25. It's a little more than 15 minutes. We'll reconvene at 10:25. And at that point in allergic contact dermatitis, we'll begin our period of public comments.

And in the public comment period, we have scheduled public commenters. Some of them have arranged for special presentations and lengths of allergic contact dermatitis with Mr. Lewis and the SAP Office. And so they'll be granted extra allergic contact dermatitis.

If you are in the audience and want to make a public comment, again, during this period at the end of the scheduled presentations, please, see Paul during the break. We'll reconvene at 10:25.

[Break taken at 10 a.m.

Session resumed at 10:28 a.m.]

DR. HEERINGA: Welcome back to the late morning session of our FIFRA SAB Panel meeting on the topic of the Consultation on Dermal Sensitization Issues for Exposures to Pesticides.

We are about to enter the public comment period. But before we do, EPA has asked -- and I think it's a very good idea -- that they be permitted to read through the formal charge questions that are addressed to the Panel. It helps to set context, I think, and to remind us throughout these two- or three-day meetings exactly what we're focusing on with regard to the EPA's scientific interest in the Panel.

Dr. McMahon, if you would like to read the charge questions to the Panel.

DR. MCMAHON: Thank you, Dr. Heeringa. They were about to be shown up on the screen.

DR. HEERINGA: While you're doing that, let me just use the allergic contact dermatitis for one announcement. The members of the Panel should have received during the break a copy of a paper by a Dr. Paul Cooper of the University of Toronto, "Comparison of fixation and leaching characteristics of acid copper chromate ACC with CCA-C." And a copy of that paper will be placed in the docket.

DR. MCMAHON: Our issue for the SAP Panel deals with the quantitative risk assessment for the induction phase of allergic contact dermatitis. As we've seen approaches for determination of the quantitative assessment of sensitization induction thresholds have been produced in the literature using results of murine LLNA and/or data from human patch testing by Gerberick and by Griem.

Gerberick proposed a methodology, as we saw for determination of a sensitization reference dose for sensitizers in consumer products, where the lower boundary of the potency category for a chemical was used as a starting point with application of uncertainty factors for interindividual variability, product matrix effects, and use pattern.

We've also seen that Griem, et al., proposed a quantitative approach using the EC3 value from LLNA as a starting point as a surrogate value for an NOAEL that could be used as a starting point in quantitative assessment.

We've also seen that uncertainty factors are concerned for the interspecies variation, the intraspecies variation product matrix effects and conditions of exposure.

So our first question for the SAP is: What are the strengths and proposed quantitative approach for determination of induction thresholds to dermal sensitizing chemicals? What other approaches does the Panel recommend EPA consider? Which uncertainty factors does the Panel feel are the most appropriate for application to quantitative methods of induction threshold determination? And what factors should be included in the determination of the magnitude of each uncertainty factor.

Our second issue for the Panel deals with the quantitative risk assessment for the elicitation phase of allergic contact dermatitis.

As we've seen, again, we've seen the concept of the minimum elicitation threshold as discussed in previous publications by

Nethercott and Basketter, specifically through spectahexavalent chromium. We have also that this concept is employed as a result of testing sensitized individuals but that we have not had an extensive discussion of the criteria for employing this concept.

So our second question for the Panel is: What are the strengths of proposed quantitative approaches for determination of elicitation thresholds to dermal sensitizing chemicals? What other approaches does the Panel recommend that the EPA consider? Which uncertainty factors does the Panel feel are the most appropriate for the application to quantitative methods of elicitation threshold determination? And what factors should be included in the determination of the magnitude of each uncertainty factor.

The third question issue for the SAP deals with children's sensitivity. As we have presented, we have data from Paustenback and

Felter who have discussed whether children are or more less at risk for the development allergic contact dermatitis. With respect to hexavalent, Paustenback has said risks to children ages 3 to 8 is not likely to be greater than adults.

And whereas Felter has suggested that infants and children may actually be at lower risk for development of allergic contact dermatitis. We've seen that data from Whorel, et al., suggest there may be issue with respect to sensitivity and age.

We also understand that young children may not have been exposed to different allergens as compared to adults. In addition, increased frequency of exposure in children may increase a chance of induction to differential allergens.

So our third question to the Panel is: Does the Panel agree that the available scientific data suggests no significant difference in the relative sensitivity of children versus adult to the induction and/or elicitation of allergic contact dermatitis? And if so, please provide scientific justification for this position.

If the Panel disagrees, please provide scientific justification including supporting data and/or uncertainties in the explanation.

Our forth issue for the SAP deals with the case study Cr(VI) in treated wood.

As we've seen data from the murine LLAN tests as well as from human patch testing studies are available for hexavalent chromium in the literature. And we know that the EC3 values indicate area doses that result in the induction of sensitization in the mouth are results of patch tests in humans show area doses that result in elicitation of sensitization in already sensitized individuals.

In our initial assessment where we sought to assess the dermal sensitization hexavalent chromium, the lowest dose tested at .018 ug/cm2 from the human patch test study of Nethercott in 1994 was selected for determination of dermal risk from hexavalent chromium.

A total uncertainty factor of 10x and 3x for use of the LOAEL and 3x for the small study population was applied resulting in a "safe" area of 0.0018 mgsqc. We've also seen that using the data of Basketter and Hansen will result in a derivation of similar "safe" area doses of .0001 and .003 mgsqc respectively.

Our fourth question for the SAP, then, would be: Please comment on the methods used for derivation of "safe" area doses using the LLNA data and human patch test data and including the magnitude of the applied uncertainty factors and include a scientific rationale in support of your position. Please comment on whether it is scientifically supportable to derive separate "safe" area doses for protection against induction of dermal sensitization as well as elicitation in sensitized individuals by hexavalent chromium.

Thank you.

DR. HEERINGA: Thank you very much, Dr. McMahon.

And, again, that was intended to set the context for presentations and for the discussion and the Panel responses that will occur later on in this meeting.

At this point in allergic contact dermatitis, we'll move to the period of public comments. And I believe that the public comment mike is set up here in the right-hand corner of the table.

And at this point in allergic contact dermatitis, I'd like to invite Dr. Michele Burgess of the EPA Office of Solid

Waste and Emergency Response to come up and present her comments.

Before I get started, I just wanted to make sure that my slides will be provided to the Panel members prior to my discussion. If not, I do have a copy.

MR. LEWIS: The slides were shared with the Panel here. Thank you.

DR. BURGESS: Great. Thank you very much.

Well, good morning, distinguished Chairman, honorable Panel members, ladies and gentlemen.

Let me introduce myself. My name is Dr. Michele Burgess. And, yes, I'm with the United States Environmental Protection Agency, Office of Solid Waste and Emergency Response, also known as OSWER.

Thank you so much for this opportunity to discuss dermal sensitization from exposes to pesticides in the environment.

I would like to take a few moments to provide some background on OSWER's programs which I hope will provide a useful back drop for today's discussion.

OSWER has two national programs that it implements. First is the Comprehensive Environmental Response Compensation and Liability Act, also know CERCLA, commonly known as Super Fund, which addresses the cleanup of hazard substances released into the environment, the land, air, and water. And the second the Resource Conservation & Recovery Act, also known as RCRA, which regulates the management of disposal of pesticides as well as corrective action of hazardous substances.

As I said, a number of pesticides are Super Fund hazardous substances as well as RCRA hazardous waste. Towards achieving a clean-up remedy, the Super Fund clean up and RCRA Corrective Action Programs generally conduct human health and ecological risk assessments. And remedial goals are developed from these.

These remedial goals are media specific and site specific and address among other things the dermal exposure pathway. In addition, pesticides which are RCRA hazardous wastes must also be managed and disposed of in accordance with RCRA regulations.

Therefore, since a number of pesticides are Super Fund hazardous substances and RCRA hazardous wastes, the cross-agency consistency on the question of dermal sensitization is an important one.

I would like to focus my discussion on the factors that impact implementation of a toxicity value towards evaluating regulating safe levels of chemicals in the environment. As I stated before, OSWER implements several multi-media programs, specifically OSWER programs are responsible for remediation and disposal of contaminants incorporated in a variety of environmental media such as wood, soil, and water. An integral part of developing an environmental hazard assessment for a chemical contaminant is the application of experimental data to the actual and reasonably anticipated environmental exposure scenario.

The question before the Panel today addresses direct dermal contact with contaminated environmental media. OSWER programs take into consideration environmental media factors that influence the availability of the chemical for exposure to humans and ecological receptors. It is important to assess the contact with the media which may render the same adverse health effect that has been experimentally tried.

Therefore, OSWER is specifically interested in how each environmental matrix variable presents similar as well as matrix-specific variables as well as those site-specific factors that will impact the estimation of the acceptable environmental area dermal dose.

OSWER will not ask the Panel to weigh in on human activity dependent factors such as contact frequency, available exposed skin surface area, or human exposure scenarios.

I will now discuss in more detail the influential media variables for wood, soil, and water. The preceding presentations by Drs. McMahon and Chen presented methodology towards assessing the toxic endpoint of hexavalent chromium and the fixation process of hexavalent chromium to trivalent chromate in a wood product.

The interest lies in evaluating whether a safe level of chromium exposure from direct dermal contact with chromium residues on the surface of treated lumber will not lead to development of an adverse effect. And that form would be either a dermal irritation and/or acute contact dermatitis.

Conditions such as pH, temperature, wood types, wood moisture content, and allergic contact dermatitis will influence the bioavailability of the chemical incorporated in the wood. In the case chromium, these conditions will determine the form of chromium that is available for direct dermal exposure.

For example, the allergic contact dermatitis and temperature are directly correlated to the conversion of hexavalent chromium to trivalent chromium on treated wood. Thus, an increase temperature or allergic contact dermatitis will increase the rate that the hexavalent form will convert to trivalent form; and, therefore, affect the human health exposure. And I'll explain why I'm bringing that up a little bit later.

In the soil media describing an

absorbed dermal dose of extractable, chromium is determined by many factors. I have divided these into three categories: soil properties, chemical properties, and other.

Soil properties that will impact the availability of the chemical to the skin are organic content, water content, and the soil type. The organic content of the soil produces an environment whereby the chemical will either be bound by the organic carbon content of the soil, and thus influencing mobility of the chemical from the soil to the skin.

The water content of the soil will be governed by the solubility of the chemical in the water. The soil water content may be sufficient to present an environment whereby the chemical is dissolved in the water and will influence the release of the chemical from the soil to the skin.

The soil type, such as either sandy,

loamy, or silty, will influence the ability of the chemical to move from the soil to the skin by inherent soil factors such as soil particle size which will govern the available soil surface area to contact the skin, thus determining the amount of the chemical that is available to be absorbed by the skin.

The particular soil type also influences what is known as the "soil adherence factor." The soil adherence factor describes that amount of soil that adheres to the skin per unit of skin surface, area. Depending on the soil type, the soil adherence factors can range anywhere from 5.4 to 61 milligram per cubic centimeter. And as per the 2001 draft review risk assessment guidance for Super Fund, Part E, Supplemental Guidance for Dermal Risk Assessment.

Another important soil property are the soil conditions suitable for the media conversion of the chemical. These chemical conversions are produced by reduction or oxidation reactions. In the case of chromium, under certain conditions, a large proportion of the hexavalent chromium will be converted to the form of trivalent chromate resulting in a total soil chromium concentration that is actually a ratio of hexavalent to trivalent chromate.

Literature sources indicate anywhere from 8 to 15 percent of total chromium in the soil is in the hexavalent form. And in fact, in 2001, the Science Advisory Panel determined that the acceptable level of total chromium in the soil should be adjusted by 10 percent to account for the trivalent to hexavalent chromium ratio.

This is important because the form that the chemical assumes, such as speciation, will influence the toxicity of that chemical in a biological system. In the case of chromium, the speciation may impact its ability to illicit allergic contact dermatitis.

Lastly, the concentration in the soil is a principal factor. The probability of a chemical transfer from the soil to the skin is directly correlated to the concentration of the chemical found in the soil.

Lastly, the other factor that may be influencing the mobility of a chemical from the soil to the biological matrix is the chemical permeability coefficient. The chemical permeability is the chemical-specific biological determinant of the amount of chemical that will be absorbed by the skin. It is mainly determined by the contents of the sweat in the skin which may influence, again, the mobility of the chemical from the soil to the skin. I will discuss this in more detail in the next side.

The last matrix that I will discuss

is water. And it incorporates many of the same matrix factors that I have previously discussed with regard to wood and soil. However, a water specific variable that heavily influences the mobility of the chemical from the water to the skin is the permeability coefficients, also known as the Kp.

The PC determines the rate of migration of the chemical through the skin derived from either experimentally measured or predicted values. The PC for chromium is dependent upon the speciation of chromium. And as, again, discussed in the 2001 Risk Assessment Guidance for Super Fund, Part E, Supplemental Guidance for dermal risk assessment, the recommended permeability coefficient for trivalent chromate is 1 x 10-3 (cm/hr), and hexavalent chromium, 2 x 10-3 (cm/hr.) These recommended values are the highest reported PC for those two species for chromium.

OSWER considers the media variables in the wood, soil, and water to be important factors in our program's decisions when determining an acceptable area dermal dose. The valuation of these values are not only matrix specific but also site specific and are one of the key factors that are taken into consideration when OSWER establishes a remedial or regulatory decision.

Therefore, the questions that OSWER would respectfully welcome input from the Panel on include: Does the SAP agree that environmental matrix variables will influence the acceptable area dermal dose to induce or elicit contact dermal sensitization in an individual when exposed to a chemical. And, secondly, please describe whether media-specific characteristics have or do not have a substantial impact on determining an environmental acceptable dermal dose for a chemical that is incorporated in environmental media.

In closing, let me thank you, distinguished Chairman and honorable Panel members, for this opportunity on input on this very important environmental topic.

DR. HEERINGA: Thank you very much, Dr. Burgess. And I think as part of Dr. Burgess's presentation, there have been several questions which are questions eliciting information and response. And in these should be taken in the context of the public comment. And I think you are free to respond to those or as applicable to the charge questions that we will be reviewing later to incorporate a response to these issues as part of that as well.

Now, are there any questions for Dr. Burgess on her presentation or any initial reactions?

DR. CHU: Dr. Burgess, I'm

interested in your presentation. There's a slide, Slide 7, you presented permeability coefficient, KP values --

DR. BURGESS: Yes.

DR. CHU: -- for Cr(III) and Cr(VI).

DR. BURGESS: Yes, sir.

DR. CHU: Are these predicted of modeled ladders or empirically determined?

DR. BURGESS: The ones that I in particular chose -- and these are the ones again that OSWER has chosen to use in their own risk assessment guidance for dermal assessments -- were actually measured values.

DR. CHU: Okay.

DR. BURGESS: But all of them measured and predicted values are incorporated in the guidance for use.

DR. CHU: Based on these values, the KP values of Cr(III) is only slower than the Cr(VI) by 50 percent. How does this permeation rate compare with the common belief that Cr(III) is not absorbed versus Cr(VI)? The common belief is because Cr(VI) is absorbable as compared to Cr(III)? Can you sort of expand?

DR. BURGESS: If I understand your question right, you're just wanting to know how those relate to the --

DR. CHU: That's right. Because commonly we believe that Cr(III) is not absorbed. That's why it doesn't pose a health hazard concern.

DR. BURGESS: Exactly. And, again, that is a concern of ours, too, that you may be having that absorbed. As you know, once chromium is entered into a biological systems, it's actually converted to Cr(III) even if it had been producing a hexavalent form. And through these measured values, we've been looking at this particular issue. And we do take that into consideration for making decisions.

Just a side note. This guidance that I'm citing from is actually out on draft public comment. And we have been receiving comments on that as well in trying to decide how to address that. Thank you.

DR. HEERINGA: Thank you. And, Dr. Chu, my apologies on the name mixup. I always apologize in advance to the panelists for scrambling names.

DR. PLEUS: In terms of the guidance that you're just discussing right now, you say it's out for draft comment.

DR. BURGESS: Yes.

DR. PLEUS: Could you provide A web link or anything along that line?

DR. BURGESS: Actually, it is provided in the background material. I think it's on the last page if I'm correct.

DR. PLEUS: That is the reference.

DR. BURGESS: Yes. There is a web link there. Otherwise, I can get that for you.

DR. HEERINGA: We can certainly identify that web link and let everybody know.

DR. BURGESS: Or I definitely will. Or if you'd like me to bring you a hard copy, I'd be happy to do that as well.

DR. PLEUS: Either one would be great. Thank you.

DR. BURGESS: Okay. Sure.

DR. HEERINGA: Any other questions for Dr. Burgess from members of the Panel?

Well, thank you very much, Dr. Burgess.

DR. BURGESS: Thank you.

DR. HEERINGA: Our next public commenter is Mr. James Aidala with the ACTA Group. He's representing the Forest Products Research Laboratory. Mr. Aidala, do I have the name correct?

MR. AIDALA: Thank you, Mr. Chairman. We're all going to be coming up.

I'm just going to do an introduction if that's okay with you.

DR. HEERINGA: That would be fine. And this would include Dr. Maibach and others as well.

MR. AIDALA: And I'll introduce our folks here.

DR. HEERINGA: The thing I would ask is that maybe at appropriate times -- and I'll let you control this a little bit -- we would have a chance for the questions of clarification or comment.

MR. AIDALA: Oh, certainly, certainly. In fact, I'm just going to do an introduction and then leave the table. I'll come back, but I'll let people that actually can be more articulate about what we're going to be presenting.

My name is Jim Aidala. I'm a vice president of the ACTA Group which is an environmental consulting firm. My previous positions in this field include, most notably, a long stint at EPA itself as a senior political appointee of the Clinton administration having the honor of closing my allergic contact dermatitis at EPA as the assistant administrator for the Office of Prevention Pesticides and Toxic Substances. And I'm happy to be here and happy to be part of the proceedings.

On behalf of Forest Products Research Laboratory, FPRL, we thank you for the opportunity to address the SAP and its examination of quantitative RA in the context of dermal sensitization issues for exposure to pesticides.

I'd like to use just a few moments now to address the context of those charges that are being presented to the Panel and then introduce these others who are joining me today on behalf of Forest Products and outline a little bit the order of our presentation for the Panel.

FPRL is seeking to obtain from EPA registration for a pesticide product, acid copper chromate, ACC. ACC has been a registered pesticide product in the United States for several decades and is used widely in Europe as a wood preservative. Product testing of ACC-treated wood demonstrates that ACC is cost-effective and is a replacement for CCA which was prohibited from use in treated wood for residential uses, as Mr. Jones mentioned earlier, as of December 31, 2003. Given the removal of most CCA-uses, commercial and residential users of treated wood would benefit from some additional choices.

In mid 2003, FPRL applied to EPA for registration for ACC which contains chromium. EPA has identified the chromium component of ACC as a potential skin sensitizer. We believe there's ample data that does exist to demonstrate that chromium poses no risk of dermal sensitization to the general population from this use. Therefore, ACC could be used as wood treatment preservative without any question as to its safety and effectiveness to the public.

The context of the SAP meeting is exposures to determine sensitizers incorporated in the treated articles, such as treated wood. And as EPA has explained, hexavalent chromium is a component of ACC intended to be used in a wood preservative formulation is being considered as a case study to explore methodologies to assess these types of expose scenarios. According to the EPA presentation, the methods developed for hexavalent chromium could form the basis for determining the approach and types of data needed to assess dermal sensitizers potentially used in products available to consumers. In other words, it's not just for this particular product and this kind of product that across the board is an arena for the potential examination for approval of pesticide products across the board.

The presentations we're making today will clarify that ACC in terms of the case study is a safe product. And although chromium is a potent skin sensitizer that can lead to reversible dermal irritation, the levels of hexavalent chromium in ACC-treated wood are so low that, like CCA-treated wood before, which also has chromium as a component, ACC-treated wood presents little or no risk of dermal sensitization to the general population.

In addition, the presentations address the local lymph node assay, LLNA, a novel and predictive method for identification of skin sensitizing chemicals where activity is judged as a function of the induction phase of sensitization. The interest in LLNA is well-founded; and indeed there is significant interest in attempting to show its utility for RA purposes. However, as we'll try and argue before you now, the LLAN approach for purpose of risk assessment has not been validated extensively. And for this reason, LLNA is not ready as a tool, we believe, for EPA or industry to rely on in quantitative risk assessment for the purpose in ensuring the safety of pesticide products.

Questions surrounding the appropriate uses of the LLAN method are not something that can be addressed through just simple application of various uncertainty factors in a RA process. The case analysis presented by EPA relying on the LLAN approach is unnecessarily conservative and, fortunately in this case, there's a wealth of data clinical and otherwise, showing that chromium has mostly been a problem only in certain occupational settings. Now simply because there's a new tool at its disposal as an analytical approach, does not mean it's necessarily ready in the precise world of regulatory decision-making. And, obviously, that's our position. That's a key issue underlying the questions on which this Panel has been asked to comment.

Relevant to establishing a regulatory threshold is to consider what segment of the population may be at greatest risk. The chromium-sensitized population is a fraction of the general population and is comprised almost entirely of occupationally exposed individuals but not solely. But with this point in mind, I wish to bring to the Panel's attention EPA's own existing policy with respect to sensitive subpopulations, and what part of the population is the basis of establishing regulatory standards. The stated policy as articulated by EPA in a March 2004 report on risk assessment principles, is as follows. And I quote:

EPA typically cannot protect every individual, but rather attempts to protect individuals who represent high-end exposures, typically around the 90th percentile and above, or those who have some underlying biological sensitivity. In doing so, EPA protects the rest of the population as well. In general, EPA tries to protect sensitive individuals based on normal distribution of sensitivities. EPA considers the most sensitive individuals where there are data but does not necessarily attempt to protect, quote "hypersensitive" individuals, closed quote.

And even with the tougher standards imposed by the FQPA amendments to FIFRA, we will show that ACC can be used to treat wood for residential use and meet the applicable FQPA and FIFRA standard. Although EPA's stated risk assessment policy is not to protect everyone, our presentation will show that the use of ACC for wood treatment will present no increased risk of allergic contact dermatitis in the general population.

Today, FPRL is bringing leading experts in the field of dermatology and exposure assessment to help the Panel's exploration of novel ways to address the assessment of risks associated with being exposed to dermal irritants. Dr. Howard Maibach, author of over 1,725 publications and preeminent expert in the field of dermatology, will address the Panel on topics related to skin sensitization, testing, children's exposures, and dermatology generally.

Dr. Maibach is a Professor within the University California San Francisco Dermatology Department and has written and lectured extensively on the toxicity to man from skin exposures and on the treatment of skin diseases. We're fortunate to have him here to present today and to provide insights that only a man with that kind of experience and expertise can provide.

Dr. Maibach is joined by Dr. Susan Youngren, also of the ACTA Group who will present on assessments specific to chromium and treated wood. And Mr. Dennis Morgan, General Manager of Forest Products Research Laboratory, an Oregon-based company that conducts research and uses commercializes products used in the production of wood and composite materials. Mr. Morgan will provide the Panel with insight into ACC wood preservative and what we like to call the world of treated wood.

Together these individuals will provide, we hope, useful guidance to you as you work your way and provide expert advice to EPA in how to evaluate the general populations exposure to pesticides that are recognized to cause dermal sensitization.

We hope that as a group our comments help the Panel, and in turn assist EPA in deliberating in a timely manner in deciding the ACC application before the Agency. I very much appreciate the allergic contact dermatitis I've been allowed today, and I will now turn to my colleagues to more fully articulate the points I've made.

Thank you.

DR. HEERINGA: At this point I have listed Dr. Maibach as the next speaker.

DR. YOUNGREN: This is Susan Youngren. I just want to ask whether you have a copy of our slides and then you should also have three articles --

DR. HEERINGA: Yes, they have just been distributed. Thank you very much.

DR. YOUNGREN: We have also just given to Mr. Lewis to give to all the Panel members a copy of Mr. Aidala's opening remarks.

DR. HEERINGA: Thank you very much. That will be included in the docket. Dr.

Maibach.

DR. MAIBACH. Panelists and guests of this august group, may I stand, Mr. Chair?

DR. HEERINGA: You may stand.

DR. MAIBACH: In my career, we don't know how to do anything sitting.

DR. HEERINGA: Okay.

DR. MAIBACH: I'd like to start by saying that, clearly, I am not a panelist; and, therefore, I have no advice for anybody. What I am going to try to do, though, is begin to get you, because the panelists presumably know and some of them know a great deal about it, to address a very complex issue.

You've heard that hexavalent chromium -- and this is probably the last allergic contact dermatitis I'll use that word in my presentation -- is a very powerful allergen in some experimental systems. But as we sit here today, the Panelists surely know that every one of them, if they're wearing leather shoes, probably has some hexavalent chromium exposure.

So what the field has been trying to deal with for a hundred years, and we are making progress, is how do we begin to look at the chemistry that we've learned and the biology that we learned to make shrewd assessments. I've given a fair amount of allergic contact dermatitis to, hopefully, titillate your curiosity with the way the field is moving. And I'll end with some very specific examples where there is suggestive data that we are making progress.

This story is full of geniuses. I'm, unfortunately, not one of them. But the field of allergic contact dermatitis has had some Albert Einstein-like brains. If you look back at what Einstein did at the beginning of the 19th century, it's inexplicable that one man could be have been so perceptive. But he was. A man from a very simple background made some extraordinary intuitive judgments.

This field for practical purposes has surely been known about for tens of thousands if not a million or more years. But for the purposes of what the Panel is looking at for the next 3 to 50 years of policy, the first breakthrough came when a very shrewd dermatologist treating a sexually transmitted disease hardly known to most of you in the audience today, but was a very important diseases like tuberculosis 50 years ago, namely syphilis. They treated syphilis with mercury. And one patient -- this is applied to the skin. One patient got a horrendous dermatitis. The light bulb went on -- I'm not sure how many light bulbs there were. This was 1898 -- in Jadassohn's head, and Jadassohn said that all chemical rashes probably were at the same mechanism. Now, that's over a hundred years ago.

As a practical matter, the real next

break through came from another enormously intuitive man who provided you with much of the data that you're going to use in your deliberations because it's the data on, if you take specialized populations going to see usually a dermatologist but occasionally an allergist, occasionally an occupational physician, and if the health care worker can't make a diagnosis on history and examination and is looking for help to try to explain what's going on and does a patch test.

People have followed this brilliant man's precept. Because in about just before the Second World War in a wonderful textbook in German -- and I believe I may have the only copy in the United States. I'm indebted to some of my Danish colleagues for it and I'm happy to share it with any of you, but you have to come to my private library to use it. I'm not even trusting it to Federal Express -- an occupational physician, not an allergist, not a dermatologist, said, look, we're looking for these unknown diagnoses. We are looking to try to understand what's going on. Let's test until we understand more than we understand today every patient in which the diagnosis occult with the same allergens. That is what is known as the routine series.

Now this gentleman, Bonneviv, who I have had the pleasure of meeting on several occasions, was so perceptive that although this was just before World War II, we still use approximately 13 of the routine chemicals that he screened within in 1939 we're using today. And it's very helpful in making diagnoses where the history and the physical examination won't do it.

So we're going to be talking, though, about the collections of the Bonneviv inspired data and the complexities of how do you use the data to make shrewd judgements. Because in the chemical, you're talking about today, it's been around a very long period of allergic contact dermatitis. So it's not a matter of a new test. It's a matter of how do you interpret what we already know.

The third breakthrough occurred again, and you will see this constantly in the history of the science of allergic contact dermatitis, in Scandinavia. A group of Scandinavians in about 1970 started a private network without any industry support, without any government support. They would meet for as often as three days twice a year at their own expense.

Eventually they wanted to change the name to sound very international. And the group still exists in a shadow form as the International Contact Dermatitis Research Group. They worked out brilliantly. In a very short period of allergic contact dermatitis, common terminology so that Dr. Foulds, Dr. Menne, and I can look at a patient.

And like music sheets, music notes, dance sheets, we can understand with a simple notation. We really know what 1 plus means, what 2 plus means, what 3 plus means. So many of these problems were worked out. And now the standard series is no longer the two dozen that it was like 30 years ago. Today the standard series -- and I'll comment on this in North America, which is presumably postulated in the confines of the EPA -- is over 60 materials that help in the diagnosis of unknown eczema.

After the International CD Research Group was formed, I had the enormous good luck -- and I have to attribute it to good luck -- to be invited to be part of the International. And as a young kid in San Francisco, and I know how little I know now, but I new nothing then. They gave me this opportunity.

I started a group in North America,

which is still going, the North America Contact Dermatitis Research Group, which has gathered a lot of the epidemiologic or pseudoepidemiologic data that you will be hearing about in your deliberations. Otherwise, the frequency of positive patch tests, whether they are truly allergic or whether they are an irritant or they are any other mechanism in a specialized population, namely the people who end up in a dermatologist's office.

Now, the strongest group that we have at the moment is the young people who didn't want to deal with the international group, namely, but who worked closely with many of them in very good relationships, started what is now the European Environmental Contact Dermatitis Research Group, and they are extremely active and adding a large amount of evidence based data.

Now in addition to these groups, if

you really want to be a scholar, we can provide you data from Portugal. We can provide you data from Chile, from all over Japan. There are about 10 of these little academic unfunded study groups that are constantly adding numbers. So you're not going to be short of numbers. Your problem is going to be the same as mine, how do you interpret the numbers.

The last breakthrough was probably largely responsible due to one of your panelists, Torkil Menne, who convinced the European community that it was worth spending resources to get evidence-based data. And in a series of studies funded by the European community on dose response relationships, which we'll go into more, of serial dilution testing and of something that we'll introduce which we think that is enormously valuable in understanding what you are doing here, actual use tests which answer many questions.

This really was a major breakthrough. And we hope that Dr. Menne is able to get the European community and maybe NIOSH and OSHA and NIH and many other groups to fund these studies because they're so powerful in the quality of the information that they portray.

Now, earlier this morning you've been told about the difference been induction of allergy and elicitation of allergy. Of course, those of you who are not fatigued from your travel, you understand that that separation is highly arbitrary. Otherwise, it has to start somewhere. That's called the induction. It's consequence is the elicitation. But obviously the same skin, the same body, the same epidermal cells, the same Langerhans cells, are involved. And all we're really talking about here is really a simplification, because it is enormously useful in toxicologic considerations, but it is the same event.

Now let's talk a little bit about the practical points in looking at the new chemicals that our government and governments will be looking at. Well, the first thing is that we do know from evidence-based observations that the higher the concentration that you apply, the more likely you are to induce sensitization. That must be kept very, very clear.

Second, once you're induced, you will frequently, but not always, react to much lower concentrations. Otherwise, once you're sensitized, once you're really induced -- and there are probably many exceptions to this -- if you get a rash with lower concentrations later on, we say you're sensitized.

Next, what can we say about elicitation. Well, you have to be induced. But it turns out for some chemicals such as the experimental allergen which is used in industry also, dinytrochlorobenzine, the first application can sensitize you. So at the site where you apply it, as soon as 7 to 10 days later, two weeks later, you can spontaneously get a new dermatitis.

So, obviously, what's really interesting is that most of the chemicals we deal with aren't that potent. And we don't fully, we don't really in any way adequately understand why can somebody deal with a chemical for 10 to 60, 70 years and then suddenly get a dermatitis. That is in the realm of the unknown at the moment, but a great deal is known. So I'm going to emphasize what's known.

Now, in this particular series of slides, I'm going to introduce some very simple ideas but that are inherent in reading and understanding the evidence for allergic contact dermatitis. It's a little bit cumbersome only slightly. I realize that, even though we tried to make these overheads large, in the back might not be able to see it. In fact, I have to put on my glasses. But I'm now going to begin to talk about dose.

In oral dosing, all of you know that we orderly describe the dose as milligrams of a dose. If it's a drug that has a fine margin, a small margin, between the effective and toxic dose, we don't usually just say take 50 milligrams. We say adjust the dose either for body weight or for body size. Otherwise, meter squared or weight in pounds or kilograms. We really need to do the exact same things for skin.

We're not yet sophisticated enough to do it for body area or for body weight, but we are sophisticated enough, both in one field that work in, namely percutaneous penetration, and now allergic and irritant dermatitis, to express all doses in mass/unit area.

It's critical that you know that

because the literature that you're going to be depending on when you advise the staff at government agencies, when the staff read that literature, they're going to be dealing with units like percent; they're going to be dealing with units like parts per million; and they're going to be dealing with units like milligrams or micrograms per centimeter squared of skin. So if you don't know how to convert that, you will get lost.

Now fortunately for those of you who are sitting anywhere but in the front, the calculations are in the handouts which are readily available to you.

Now, the next point that I'd like to emphasize -- could you just go back one second? -- is that in many of things that you've heard about this morning, we're talking about cutoff points. What is the threshold for allergy? We deal with this intuitively. And, certainly, people like one of your panelist at the FDA who dealt with the skin part deal with it routinely, many compounds are sensitizing in huge percentages of the population.

Let me give you an example, benzyaleal peroxide is the most widely used the topical agent in the treatment of relatively mild acne. It was available first as a prescription. Now in almost all of the world -- I'm sure there's some country that's an exception -- over the counter. When you put benzyaleal peroxide in some of the tests that you've heard about, you will sensitize one out of every two panelists.

Now, Dr. Jacobs wouldn't be very happy with our using BPO if it sensitized 50 percent of all the people who used it. It clearly doesn't. But that lead then to very careful examination of many phenomena that are involved.

Now you may say, well, Howard, how

the heck did you -- were you responsible in any way for using a chemical that sensitized 50 percent of the people in a six-week test? Well, luckily, BPO was used before I came around the scene. And only after it was around and we were trying to develop data bases that we could interpret, did we do the human test.

When we did the human test, that's what we found out. And we were terrified. So we then did careful epidemiologic studies looking for sensitized people. And we do think that benzyl peroxide sensitized some human beings. But we think the rate is somewhere between 1 in 10,000 and 1 in 100. I hate to give you that large of range, but that's the knowledge of our epidemiology. So we're going to be talking a great deal about what we know about these threshold levels.

Now, when we talk about a dermal dose metric, I'm going to try to take you as how to go from the patch test data to what is typically presented in either percent dose, or if it's a proper scientist and I guess I'm not proper because I make this mistake all the allergic contact dermatitis, in molarity. You have to realize that there are different types of patches. We'll be talking about those. And you can put various amounts of material on the patch.

In the old days, and many laboratories still, like creatures of habit like the old way, we took pads, usually nonwoven rayon was the most common pad. We didn't always cut them to the exact size. And then we dosed them. Today most of the more sophisticated work that will help government agencies are not done with a little pad like that. They're done with chambers which with proper pressure and a proper adhesive do two things. Number one, they give you occlusion which seems to be necessary to make these tests work well. Number two, they limit the area so you really know something about dose.

In our irritancy testing, this was the breakthrough in getting reproducible data, limiting the area. It sounds so simple. I'm sure a lot of you are saying, Howard, why didn't you do it in 1898. First of all I wasn't here in 1898. And second of all, many simple things are simple once you know them; but they're not simple before that.

Now, we now then that you need for elicitation of sensitization a certain surface area. We'll talk more about this. And for induction of sensitization, you need a certain surface area. If you go down now to the middle, it's mass/unit area. The mass is usually explained in weight or involvement in volume per centimeter square.

And so if you see then that next line, for those of you who can see it, and it's in the handout, it allows you if you know the charge what's put in the chamber, if you know the surface area and the people who make them tell you the surface area if you don't have a ruler, and you can then simply convert everything into what is the threshold dose or what is the response dose in micrograms or microliters per cm2.

Here is particularly a little more complicated example. Again, I'll break my rule about not talking about chromate. But when you look chromate, you can express it in terms of potassium. So in Europe, the patch test concentration is one half a percentage of potassium dichromate. That is, obviously, to all of you in this audience exactly equivalent -- it's another synonym -- for 5,000 parts per million of are potassium dichromate.

So if you take the chamber that is most widely used internationally to make not induction, but to make the diagnosis, it's a little aluminum chamber developed by the late

Vaco Perola, and commercialized under the name of the Finn Chamber because he lived in Finland, obviously, a great Dane.

When you take that, if you really stuff it, and we usually don't. We usually load it about with about 17 microliters. But to make the math easier, 20 microliters applied to the surface area in the patch is a 0.5 cm2. And you then can do your calculations. So for now on, whether you read percent, parts per million, or ug/cm2, you can go from study to study to try to determine how to use the numbers that you've got.

Now, there have been some technical advances. This is one that with Torkil Fisher, who is a guest scientist in our lab that we worked on, I never received any royalties, so I didn't sign conflict of interest comment because I'm not on your panel, but I waived all royalties so I could talk about it in public. That's how clever we thought it was 20 years ago when we did it. And the idea is clever. It just turns out it hasn't helped us very much.

When you look at one of the sets of data that you're going to be shown with chromate, it is with another test, which is meant to be easier for the patient, for the doctor who applies it, or really it's the nurse, and is meant to be more scientific. And it is more scientific in terms of pharmaceutics. It is simply the compound, the allergen you're looking at -- and there are only two dozen available, so it doesn't help you with the other several hundred allergens -- and it's put on a piece of paper where you can get a homogeneous distribution.

Next it is prepackaged, and it's sold so the technicians simply opens it like they open a stick of gum wrapped in paper. And you put it on the back. And here are the metrics. This is 23 of potassium dichromate, 6.7 micrograms per patch. You've got the surface area. And then you know that the total dose 8 micrograms of hexavalent chromium per cm2. These are the sorts of simple calculations you need to determine the relevance to your questions or to the Agency's questions of the new induction and elicitation data.

What do we know about the relationship then now that we've gone to mass per cm2 of inducing sensitization. Well, we don't know as much as we would like to know. And I'm going to share with you in brief the concept. I'm going to give you a reference for those of you who want to read it more. But for those of you in the audience who are going to be solving the problem for the future, I'm hoping that you're going to be do 10 more experiments because the data base is relatively small.

The reference that I'm referring to

is Upadhye, Contact Dermatitis 27218. What this young medical student did was very simply was to look -- and the indexes don't help you -- hand searching, speaking to colleagues in dermatology who know the literature, what do we really know. Well, I'm going to give you some examples.

In the early 1930s, Schnitzer, an American, really asked the right question. And this is what he found out. Just remember now this is only 30 years after the idea of allergic contact dermatitis was proposed and it was before Bonneviv told us to use the routine series.

What he did is he took a group of guinea pigs described there as A, B, and C. At 1 percent applied to the entire guinea pig, he sensitized 13 of 50 guinea pigs. That's a pretty good number because he used a great deal. He was the first one to ask the question: What is the relationship of mass/unit area.

He then did the exact same study. But he only applied it to a part of the guinea pig. It happened to be 4 or almost 5 cm2. And he sensitized the same number of animals. Well, where did that lead to today in terms of mechanisms of allergy and practical ramifications?

Well, where it lead to today is today -- and there was some brilliant guinea pig studies done by the late Fray and Dewark in Switzerland -- it lead to the idea that you've got to get a critical mass to the epidermal cell, a critical mass to the Langerhans cell, and a critical mass to the lymph node. When you look at the data that you're going to be shown in the days, weeks, and months and years to come, you have to really look then do you ever get the critical mass to a small enough area that you're going to induce allergy.

Now, my belief is that the reason we are able to deal with many allergens as successfully as we deal with them is we never -- and I'll give you some of the exceptions -- get to that critical mass. And that our risk management is, if we need to use allergenic chemicals, if they subserve a human need, well then we'd want to get them to a dose that does not induce sensitization.

Now this was the early 1930s. And in the next slide, I'll give you another example because, later on Albert Kligman at the University of Pennsylvania -- I don't know where he got the intuition -- but there was lag period of 20 years before the second experiment was done. He took a chemical monobenzyl ether of hydroquinone.

For those of you who read the National Inquirer, which happens to have the largest circulation of any paper in the United States, but I've yet to find anybody who will tell me that they read it. This is the chemical that has been alleged to have been used in a very well known American performer to bleach the skin. It is very minimally used in the United States. But that tends to introduce -- you get some interest at least in medical students.

With monobenzyl ether of hydroquinone, Dr. Kligman went from the guinea pig of Schmitzer, because there could be species difference, and he applied to one forearm, 3 grams of 20 percent MEQ and sensitized 13 percent of the population.

When he took the same material, which is a trick because it's hard to get 45 grams of anything on you. I guess Dr. Kligman was very dedicated as a young scientist. He spread it on. I can't get more than 30 grams on most people. Maybe he had large volunteers. He didn't tell us that. He applied it to the whole body and he sensitized nobody.

Again, the principle is it's mass/unit area. It's concentration. I hope that's clear. I wish I could give you 35 more examples. I can't. The experiments haven't been done. What has been done, though, is in the reference that I gave you. And so we'll go on.

The next slide is simply another example of another set of experiments again summarized in the same paper. We added the statistics that weren't done. The studies were done so long ago. And again you find that there is a threshold dose. And here is it with four compounds.

Now, I'm going to briefly comment on children. Because one of the things that I've learned about being here today is clearly I've got to work on this some more. But I'd like to try to put some of the numbers that are out there into perspective.

There are very few bits of data in my mind that are easily interpreted by ordinary people like me because I'm not Albert Einstein. Perhaps the most interpretable, but even this isn't completely interpretable, is a study in children in which one of my colleagues, now retired for some years, was interested in preventing poison ivy, poison oak, and poison sumac. It was one of his lifetime's works.

What Dr. Epstein did is he got ahold of one of the many chemicals in these groups of plants, PDC or pentadecyl catechol which is one of the allergens. And he tried, because he was interested in a vaccine so to speak. He was trying to prevent allergy. This is IRB's, but using informed consent as was done in those days, three groups.

What I would like you to see and this isn't a perfect experiment because some of these children could have been sensitized with the plant and not known it before. So it's a weakness in the study, but it's the best purposeful data that we have. You'll see that in the infants under one in sensitized with the same dose, 30 percent. From 1 to 3 years, he sensitized 50 percent of 24 children. And from the age of 3 to 8 years, he sensitized 78 percent of 37 children.

Well, how can you interpret this? Well, you can interpret this in a way by saying easily -- you can glibly say that forget the fact that they could have been exposed and the older ones might have had more hidden exposures than the 1 year olds or the 6-month olds who weren't crawling out of the bushes yet. You could say that children are relatively protected.

In my view, that would be an over statement. But you probably can say that for one chemical, not every chemical because we don't know it. For one chemical that maybe children have a less-developed immunologic system. Please don't ever quote me as saying that as a fact. It's a working hypothesis.

The only other experiment that I know of, and this is a mea culpa, in the 60s with two medical students, the senior one was Walker and the other one was Smith, we sensitized several hundred schoolchildren getting ready for their physical examinations to go to summer camp and their parents. We were interested in another question. We were interested in the question: Is there a genetic predisposition? Today I wouldn't ask such a silly question. There's a genetic predisposition to everything, I suspect.

When we did the study, we found out that with the experimental allergens we used, and we chose something that they would never have been exposed to, to experimental allergens that aren't used by ordinary human beings. One was DNCB, dinitrochlorobenzene.

The other was NDMA. And we showed, yes, that if a mom and a dad or the punitive mother and even the more punitive father were sensitized by this application, the children were much more likely to be sensitized and vice versa.

Now that I realize that everybody is interested in children, we're going to go see if those 1965 or '68 data books are still available so we can see the sensitization rate in children versus adults. That is, unfortunately, what it's going to take. Because in the other experiments just patch testing, there were two variables that could not be mentioned in the overall this morning.

One variable is we don't know enough about the role of irritancy of a patch in a four year old compared to a 40 year old and an 80 year old. They could be profoundly different. There are studies done in our lab comparing people from age 20 to 30, that decade of life, to people 70 to 90; and there is a huge difference. You would think that the older you got, the more easily it would be to irritate skin.

But with the model irritant we used -- we didn't study 10,000 irritants. It was the surfactant sodium laurel sulfate. The older people reacted less than the younger one. There seemed to be something in evolution that seemed to protect you.

So when we do look at the patch test data, such as the Whorl paper that you heard earlier this morning, it's very difficult to interpret until we know that irritancy data. Just as you think about the difference in surface area between a four year old and some of you six footers in this room, there could be differences just from that.

Now in the next slide, I give you a reference, a lovely Thai professor of dermatology, spent a year in our laboratory. For those of you who cannot pronounce his name

-- nobody in our lab could pronounce it. So he is known by his nickname, Charchai. Charchai in contact dermatitis reviewed all the literature including this data of Epstein's. And all we would conclude is that the data is weak.

The strongest experiment is the Epstein experiment. And that on balance, all we could say, until more information is generated probably from purposeful sensitization which is not easy to get people to do, that children at least in the data that we saw are very much like adults.

Now I'd like to emphasize another critical issue in interpretation. In much of the data you've heard about in order to get answers easily in small populations we have to use trickery. The trick we use is we apply the chemical with occlusion. Naively, decades ago it was believed that the reason this worked is that it drove more of the chemical into the skin. I won't get a diversion today.

But my colleagues who are very knowledgeable in this field, will tell you we now know, now that we not only do biological experiments but flux experiments, when you measure penetration, many chemicals do not have increased penetration with occlusion.

But we know in man that, if you want to put a single application on for many chemicals and get a positive that will give you a clue to allergy, you need to occlude it. The mechanisms are not completely understood by any means. One of which was thought to be penetration, but it is not only the explanation. There are many other things waiting for people like you to figure out.

In the guinea pig and in the mouse, this is not necessary. We don't understand the differences. If we had to make up an excuse, a reason for a medical student, we'd say the mouse skin and the guinea pig skin was more permeable. Unfortunately, that's not true. There are parts of the guinea pig skin that have very similar permeability to man. But medical students need to be given quick answers before they get too terribly smart. They're always cleverer than their faculty.

Now, let's talk about some of the things that have happened that might help you in your evaluation of the data that's presented to you. Well, one of them is most of the allergens that we test today, except for the TRUE Test are suspended in petrolatum. If it doesn't have solubility, this is easy. It's much easier to deal with petrolatum on a little baby patch than it is water.

But, please, remember that in the few studies that have been done, that the literature up to 10 years ago, there could be as much as a seven-fold difference between one patch and another in the amount of actual nickel that was in the petrolatum or Vaseline.

Obviously, in science, a seven-fold difference is substantive. It has to be dealt with.

So when you look at the patch test epidemiology, you have to keep that in mind. And when you look at a given patient, we look at a given patient, we have to keep that in mind.

I'm happy to say once that was published, the manufacturers are now doing a better job. We spot check this for one allergen three years ago with Hosteneck in our laboratory and the variation was down dramatically.

Next, let's talk about pharmaceuticals, pharmaceutics. First, clearly we express, at least in the T.R.U.E Test, the dose in mass/cm2. At least in the TRUE Test, which is a very small part of what's out there, only two dozen materials, we have gotten fairly homogeneity even in petrolatum. If the laboratory is looking for homogeneity, they really can overcome the great problems of a decade ago.

Let's talk about reproducibility. Because if you have any confidence in the numbers that you're looking at to make important policy judgments, what can we say about sensitivity and specificity. I'm not going to give you all of the references. I'll simply say that 10 years ago we were very unhappy with our reproduceability. Otherwise our ability to get the same answer on the left-hand side of the back and the right-hand side of the back.

I'm happy to tell you that we have a paper in press now that, if you have the same grader, the same technician, putting on the patch, we're now able to get left-right 95 percent concordance. But you're going to be used data that was not developed just by one laboratory. You're going to be looking at data developed by many laboratories. And you could well make it a subtask of a committee to look at the lack of reproduceability in the older information. I'm always interested in solving the problem for today and tomorrow. I think it is largely solved.

When you read the literature on sensitivity and specificity, please understand something. That unless you are a guru in this area or you have a direct access to Moses, Mohammed, or Jesus, we don't, except for a very few exceptions, know how to really define sensitivity or specificity because of the complexity of clinical allergic contact dermatitis in man.

We can do it beautifully in an experimental animal. We can do it beautifully in human beings that we sensitize. But when a patient walks in the street with an unknown eczema and is patch-tested by a dermatologist with 60 materials and has 3 or 5 positives, we all too often cannot determine sensitivity and specificity.

Let me give you an example. When somebody is patch-tested to the routine series in most of the world, they're tested with something call (inaudible), one of the hair die chemicals. It sensitizes a certain number of people. If you take a look at those people who are patch-test positive, many will tell you, oh, yes, I die my hair all of the time. Well, how are we going to deal with the sensitivity and specificity there because the gold standard is the clinical disease. They don't get the clinical disease.

Now, there are many explanations, probably the most important of which is, they don't get enough through their skin or they're not sensitive enough to get the clinical disease. Even in the best use tests which we'll be talking about, when we're almost certain that the people are allergic, because we only use limited dosing in the use tests, almost half of those people will never give you a positive use test. So when you look at sensitivity and specificity in your data, keep this in mind as you look at every data mass.

Now, I'm going to bring in another subject now which may be a little bit peripheral to some of your interest, but I think central to policy in the future. I would love to define allergic contact dermatitis in man mechanistically. I know or believe it is Type 4 Jell Coombs hypersensitivity. It's not usually Type 1.

But I know that if I try to passively transfer with white blood cells to man, this has never been convincingly done. So until we develop new laboratory insights, which we don't have now, the definition of allergic contact dermatitis in man is really not mechanistic. It's operational.

The operational definition, and some of you might have seen our papers on this, is to simply say that many patch tests we don't know how to clinically interpret. I've simplified the algorithm for you here. If someone is patch-tested to mashed potatoes and is positive, do they get a rash when they handle mashed potatoes. Well, since I know of nobody who is allergic to mashed potatoes, I don't think they do. So you need the history that correlates with the patch test.

For most allergens, you need a clinical outcome. When you remove the allergens, with a very few exceptions, you expect the person to get well.

Next a very valuable new tool, enormously expended in the European community, and Torkil Menne will be telling you a great deal about this, is the use test. The patch test is artificial. It's a tiny area. It's occluded. The occlusion adds to irritation. The patient and the doctor gets a great deal of information in setting risk assessment.

And you're going to be looking at this in the future because what you're really interested in is not what happens under occlusion but what happens in use. Because use then brings in the percutaneous penetration and many other biological events that the guinea pig and the mouse do not bring in.

The use test is simply -- it's gone through generations. It's now reasonably standardized, applying the material at one or more doses to one anatomic site. It's a fair amount of work. Once or twice a day in our laboratory due to some work from Dr. Menne's laboratory, we now go up to 28 days. But, please, remember if you look at some of our publications 10 years, we stopped at 7 days. We didn't know.

But even if you take most of the allergens that we think are allergens, we have yet to get up to a hundred percent of the people who get a clinical disease. Again, we think it's probably subthreshold.

Now, I'm going to talk now about how a number of different groups in the world are beginning, not as rapidly as we would like, to look at new ways of risk assessment with allergens. I'm going to start by saying that whenever a new chemical is given, we wouldn't dream of testing it without looking into the chemistry and the biology. The quantitative way of doing this, and it was done qualitatively in the 30s by some brilliant people, the qualitative way today, of course, is called QSAR, quantitative structure activity relationships.

What is the value of that in setting policy? Well, the value is it tells you so much. And I'll just give you one example. If you look at related chemicals and you know they've been used in man, what has happened. It's even richer if you know the doses that was used in man. What is the experience in the lymph node? What is the experience in the guinea pig? And it even helps you in some chemicals if you don't know the patch-test concentration and you don't have the facilities for working it out on human volunteers, you can often make a shrewd assessment by just looking at closely related chemicals.

Now, let me give you an example that I've been through at least 15 times in my career and I suspect will occur another few times. We use large numbers of quatinary ammonium compounds. You guys, you women, you use them too. If you've ever used Zepherin to clean your skin when blood is drawn, if you ever used any of the first aid creams to clean your skin if you've cut yourself, if you've ever used the materials that soften fabrics in your washing machine, if you've ever, in the women, used anti-stat so you're going to have beautiful hair days, you've used quatinary ammonium compounds.

When you look at the QACs, if you put them in these various tests, they're almost always strongly positive, suggesting that they're potent allergens. But, in fact, if you know the biology, if you know cutaneous biology and dermatotoxicology, you'll know that a very, very shrewd Swedish investigator in the 60s showed that benzylcodium chloride, as an example of the group, cannot be patch-tested with normal controls. If you take a hundred controls, which he did, he found out that a dose that was negative in 70 of them not only produced redness and swelling in a few of them, but in a few people it produced blisters. So it doesn't have a normal distribution of irritation.

So the reason I bring this up is that there is so much human experience, that if you take advantage of it, not just reading the abstracts, but really read the observations of the shrewdest observers we've got, many of the things that seem silly in dermatotoxicology begin to make sense. Benzylcodium chloride is only one such example.

Now I'm going to briefly go into some of the principles of the predictive testing. The first test is named after a deceased FDA official. He lived into his 90s. He devised many tests. He was another Albert Einstein like Jevelin (ph.) at the agency. Sheer intuition. He had no data. All he did was speak to Carl Langsteiner who was just about to win a Nobel Prize for figuring out how you can safely get a blood transfusion.

Langsteiner was dealing with leg sensitivity. Langsteiner simply suggested to Draize, just inject the material because that way you know it penetrates a group of times, wait a while, and challenge. It's quite interesting today that there's one laboratory

I know -- there is only one left that still uses it except they challenge topically. You can use this test and get all sorts of information. The test is no longer used. It's still an official FDA test. Nobody bothered to remove it from the list.

And you can actually do multiple doses so you can determine the threshold for induction and you can do, if the animal is sensitized -- it's the guinea pig -- multiple doses and get elicitation. It's of historical interest, but it would work brilliantly. It's just not the mini skirt of the year.

The second test that came along, Ed Buehler, who is living in retirement in the Cincinnati area, working at Proctor & Gamble for many years, said that, well, why inject the material. Why can't you just put it on the surface of the skin. So all the Buehler test is simply repetitive applications like the Draize test with occlusion. And he gives you great recipes and great details exactly how you can occlude it. Very few people who use the test follow his details. So if you get a false negative, he says it's you just didn't occlude properly.

Next you do it several times. A waiting period like in the Draize test. You challenge it. This is a dose response assay. In our laboratory, I've dosed many groups of guinea pigs at multiple doses to induce, multiple doses to challenge. It clearly is dose-response related for induction and elicitation.

The next person to come along was in the 60s, sat down. He studied the work of Draize. It's the late B. Magnusson working in Al Kligman's laboratory. He then went to Cincinnati and spoke to Buehler. And so Buehler had him at the occlusion. But he also knew, which is not so clear today, that irritation sometimes, but certainly not as is implied always, increases sensitization. So we added irritation with sodium laurel sulphate.

And then, because he was an educated man, he knew that was going on in the vaccines. And so just the way the human vaccines have adjuvants in them, the adjuvant that he used was Forines complete adjuvant, which is mineral and tubercle bacilli. And you can sensitize more animals. And in his little textbook he gives you some of the examples.

The Magnusson assay is still done in some laboratories in various parts of the world. It is usually thought to be more sensitive, meaning you can sensitize more animals. But even that isn't clear today with another 30 years of history.

The last test which probably is the only think, Torkil, that you might not have heard of here so far, is my favorite test of all of them at least in our laboratory. A very shrewd Czech intuitive dermatologist working for Hoffman Larouche and Jivodan in Switzerland, now in retirement, said, look, all of these tests have so many artifacts, can we use the guinea pig in open applications, no bandaging, no occlusion, no injections, and get answers.

He was the first one when he first wrote this up to stress dose. These are open applications repetitively, challenge with open applications, and multiple dosing. Since the guinea pig is large enough, you can do several doses in the same guinea pig. And with the OET, which only a handful of laboratories in the world use, you can gather irritancy data as well as sensitization data, threshold for induction, and threshold for elicitation.

So I would submit that before we discard guinea pig testing worldwide, that a few people study the massive literature that has been built up. It is still very useful and will solve problems that will not be solved with any of the other assays.

Now, when Draize went to say Lansteiner, he again, being an Albert Einstein, figured it out. What he did simply is he put multiple applications on the skin, 9 or 10 over three weeks, a rest period like you have in the guinea pig, and a challenge. The Draize repeat insult patch test is still widely used, widely recommended by the FDA. And in many countries it's widely used.

There are two tricks to it. Draize didn't know that you needed occlusion in man. Boy, that's a minor modification. Secondly, he didn't know, but we now know, that, if you use the use concentration, you often get a false negative. You have to increase, as you do in many toxicologic assays, the dose to get the right answer.

Now, I won't comment very much about

the lymph node because you've heard a greet deal about it. I would only suggest two points in brevity. First, I would like to simply say that Dr. Kimber, who is the driving force behind much of this, is very, very careful when he lectures about it and writes about it not misusing a very clever assay. He clearly tells you it is not for elicitation. It doesn't measure elicitation. You can get no dose information about elicitation. And, secondly, he cautions you about oversimplifying risk assessment with it.

The second thing is, if any of you do use the local lymph node assay, I would encourage you not to read the summaries or abstracts. I'd go to the original ICCVAM report which validated it. And I'd look at all of the publications since -- and in my case, the unpublished data is more interesting than the publications -- to see how many cases we have.

And it's clearly stated in the report where the sensitivity and specificity are not any where near 100 percent. There are so many exceptions. And there are so many more being discovered that it must be taken in total context with the rest of the data and not isolated and then denigrated because of the isolation.

Now, I'm going to briefly talk about the literature of the gold standard. What is allergy, allergy contact dermatitis in man. Well, we, using the cancer model of the World Health Organization, IARC -- and Dr. Menne and his colleague Diane Wilberg, have also written on this -- believe that, like cancer, we know only fortunately of a very few compounds that produce cancer in man where we know of a thousand compounds that produce cancer or tumors in animals.

So what IARC has done, they have tried to find a way, how did you deal with all of these animal positive studies. Well, we've developed a similar system for doing evaluation of the dermatologic and allergic literature on allergic contact dermatitis. The reference is Benezra, Journal of Investigative Dermatology. And, basically, what we do is you look at each of the factors. What are the controls? What is the clinical data given in the presentation?

By doing this, you can quantitatively or qualitatively make an assessment. We use a six-point scale. Zero we believe the chemical is not an allergen in that publication. If it's five, I'm willing to swear on every Bible there is that it really is an allergen. But as a practical matter, we do this with every journal or paper that comes out, we rarely find papers that reach four or five. Maybe one or two or three a year. Most of them are down at the zero, one, two, and three level.

So if any of you are going to work in this and begin to interpret the best gold standard, what's happening in man, I would strongly suggest you make a quantitative assessment of ever bit of the data.

I'm going to talk very briefly about the epidemiology of allergic contact dermatitis. Torkil Menne, when he was a child and I was much younger, made the mistake of writing a paper about this. And it's really a very useful paper, Torkil. But, obviously, there is a great deal of confusion.

Most of the epidemiologic studies are aimed at people walking into a dermatologist's office and now being tested with up to a hundred materials. Many of the positives do not connotate that they really ever had allergic disease. It is a positive that needs to be interpreted. Maybe they developed delayed antibody, but they never developed diseases.

What this Panel is talking about in helping going forward, we're trying to prevent, not necessarily antibody; we're trying to prevent disease. And a simple example is, since I'm a free blood donor for many things in our laboratories, I have all types of antibodies to penicillin because I received impure penicillin as a kid and as young adult. But I can tolerate penicillin without any difficulty. You have to separate the laboratory aspect from the clinical aspect.

Now, what are some of the reasons that we get positives that are not clinical disease? Well, many of the materials that we patch test with, including metals, are right to get a single patch to relate to the clinical diseases, we're near the margin of irritancy. So specifically with chromate in Europe, they use a half a percent, because most of the European dermatologists get a years training. In the United States, the North American group, recommended half of that, a quarter percent, because we don't give our dermatologists very much training in this area unless they take a fellowship.

The excited skin syndrome, we used to think that irritation was local. But, in fact, if you got a little hand eczema here, which one out of 20 European-derived people have, or if you have got three positive patch tests on your back, you presumably release chemicals, presumably cytokines, and then skin elsewhere in the body suddenly becomes hyper-reactive.

How do you know that? Well, you just simply -- and we do this all the time probably in 30 percent of the patients we test. You wait two or three weeks; repeat the patches one at a time; and 30 percent of them disappear.

There's a huge difference when you

read the literature, you want to know where was the patch applied. Because the late Magnusson and Herzel showed 40 years ago that there is a two-fold difference between the upper back and the lower back. So at the same concentration, you're going to get a very different answer if the patch is at the upper back or lower back. All of these are the sorts of things that, if you really want to work this area, paying attention to these details are requisite.

Other factors, genetics. I told you that in one study there is as, as you'd expect, with two experimental allergens, a genetic effect.

Next, age, it is age related. We don't know as much as we'd like; but we know that, at least for irritation, very old people, and now I'm defining it as above the age of 60 to the age of 90, are less reactive than younger ones. They are also less reactive to allergens. That has to be factored in when you examine the data.

Disease, patients with lymphoma are hyporeactive and we know a little bit about the mechanism. But if you're people like Dr. Jacobs who are dealing with leg ulcers, leg ulcers are the best adjuvant, much better than Forem's complete adjuvant, for sensitizing. We don't know the mechanism. It's probably multifactorial. Put a chemical on a leg ulcer, and you're going to sensitize to the weakest of allergens. Again, that all needs to be brought into the risk assessment.

Now, I'm not going to say that I'm an expert, because I'm not. I will say that I'm experienced. So when I look at trying to help people in our lab and elsewhere try to make judgments as to how to use chemistry efficiently to help man and animal, I basically spend just as much time looking at the QSAR as I do doing any study that I do.

We do the local lymph node assay. We do human assays. We do diagnostic patch testing. We do it all. I still spend more time with a new chemical and an old one, looking at what has been learned. Jadhasson got us started. I look at the animal. And I look at the clinical data and epidemiology, or as strong as sit may be, and then try to make a weight of evidence approach.

Now, in the last slide, I'm just going to bring you two more references. We really are beginning to make some improvements. Otherwise by judging the correct mass/unit area, and the reference is Wesley, a medical student in our laboratory, food and chemical toxicology for 357. We do have examples. And I'll go into it very briefly where clearly we're improving.

The data isn't perfect, but it's looking good. First, from Denmark, we had Sweden, the data with chromate, adding ferrous sulfate to cement -- not in the United States, in the countries where it's used -- the rate of chromate cement eczema allergic contact dermatitis is decreasing. It's not a perfect experiment, but it's good. There's a doctoral thesis from Denmark that will help you.

Second, a group in London has monitored. They test many, many patients in their system. And they've monitored two groups of chemicals. One group is our fragrance chemicals. As people are learning to use fragrance chemicals more appropriately, at least in one center, the rates seem to be going down of new sensitizations.

Another one is nickel. Dr. Menne was instrumental in legislation in Europe changing the exposures to nickel. And clearly, Dr. Menne told me -- I don't know if he's published it yet -- it's uncommon to see new young people in Denmark sensitized to nickel. Another triumph.

The same group in London studied some of the rubber chemicals that go into rubber gloves. Those rates seem to be decreasing. So really sort of the bottom line is that I think we are beginning to make progress because we're beginning, only beginning, to understand some of the principles. These principles are adding to uncertainty.

The last reference that I'll give you is Brukhman, B-r-u-k-h-m-a-n, Food and Chemical Toxicology, 391125, because this particular paper has the most complete collection of dose response clinical and patch test relationships that might help you in your deliberations.

Now, I left out a few things that came up this morning that I should of thought of yesterday, so I don't have any overheads.

First, really in people who work in this area, I know it sounds, the principle simple, but the devil really is in the details. When you look at the data, you really have to know how it was produced.

Second, please don't think that studies with chemicals that we know a great deal about and we've studied 15 times and we finally by get it right tells you that with a new unknown chemical, because you're setting policy for the future, that we're going to get it right. In many of the studies, we've known the chemical is an allergen in man. We've tested and tested and tested until we finally got it right for that chemical. That does not predict that we are going to hit it right the next time.

The weakest area, but we're making progress in this, is the area of exposure. Something applied to a leg ulcer is going to be a very different risk that something in a shampoo. But please don't think that necessarily in a shampoo or in a soap is going to wash off. But if it does wash off, you're clearly going to get a smaller dose. So the exposure and the percutaneous penetration data clearly need to be further developed before we are really going to understand it.

Now just to give you a challenge, and, hopefully, my dermatologic colleagues are going to simplify, give you the answer, give me the answer, we've started testing with a chemical that we thought was largely inert. We're testing now with gold salts. Gold salts are the second most common allergen in North America at the moment in terms of patch test cell mediated antibody. But it's almost impossible, it is rare, to find anyone who seems to have a clinical disease to gold.

Now, obviously, for investigators like me, that's a challenge. But I think it's also a challenge for you. When you look at the data, the techniques that are being recommended that out there, you always have to look, what does the demonstration cell mediated immunity mean to a individual population and to the patient.

Ladies and gentlemen, thank you very kindly. I hope I've stimulated some interest in where this field is going. If there are any questions, I would be happy to attempt to answer them. If not, I'm sure my colleagues will be able to answer it.

DR. HEERINGA: Thank you very much, Dr. Maibach. And I'm sure you've stimulated some questions. Dr. Handwerger.

DR. HANDWERGER: In my practice of pediatric endocrinology, I see many, many children three to eight years of age who have eczema. If they don't have eczema, they have got bruises all over their body and lower extremities. How does eczema in these children affect their ability to become sensitized to chromium or other factors? That's my first question.

DR. MAIBACH: Should I handle them one at a time? I'm not Albert Einstein, unfortunately.

Did everybody hear that? I'll repeat the question. In a pediatric endocrinologic, many patients atopic eczema, all sorts of rashes. What do we know about those types of dermatitis and their proclivity to allergic contact dermatitis? Is that a fair paraphrasing?

DR. HANDWERGER: Yes.

DR. MAIBACH: Okay. Intuitively, we know the answer. So I'll give you the intuitive answer. And then I'm going to give you what we really know because they're different. Intuitively, you must think the way I thought, that the damaged skin had to lead to an increased incidence, frequency, of new sensitizations. I mean that's really intuitively.

Because intuitively, if you didn't

know anything about the experiments in in vivo percutaneous penetration, you'd think you'd be delivering more chemical; and you'd also think that the dermatitis is releasing the cytokines which are essential in both Type 1 and Type 2 hypersensitivity. That's the theory.

Let's take a look at what we know about the practice. The practice is very unclear. Yes, certain people with atopic dermatitis do get sensitized. But, in fact, to many allergens, the best one that's been studies happens to be the poison ivy, poison oak chemicals. They have a decreased rate of sensitivity. So the intuition and the real human biology, we have a lot more to learn.

As a practical matter in my treatment, in my evaluation of resistant etopics who don't get well with dermatitis, we do look for allergy. They probably are partially protected.

DR. HANDWERGER: The second question

I have relates to cross-sensitization where exposure to one compound may increase your elicitation to chemically related compound or perhaps even a chemically unrelated compound. Can you comment on any aspect of that?

DR. MAIBACH: I'll comment on in general and in specific. In general, it is a devastatingly difficult area to work with in man unless the man, the human being, is exposed to a very unique type the chemistry. So when you look at our clinical reports, let's say with anything, you have got to look and say, if there isn't clinical data presented, did they really get a dermatitis; did they really have a use test. It's often uninterpretable.

You can study it, though, easily in guinea pigs. In guinea pigs -- and this work has been done with metals, and I can give you the reference. It's a book called "Metal Toxicology." And there is a chapter on skin by John Bergern of Stockholm where he gives a dozen experiments that he and his colleagues have done.

What he does is he takes nickel and cobalt, getting the purest nickel that he can get his hands on, which is not, unfortunately, 100 percent nickel. And then after they're sensitized, challenges them with both. So there is a small body of data that helps in this area. But it's the challenge from the future for people like you to encourage us to do more of these experiments. Is that responsive to your question?

DR. HANDWERGER: Yes.

DR. HEERINGA: Dr. Meade.

DR. MEADE: I wonder if you'd mind commenting. You somewhat advised to the Panel and the audience to look with a little bit of skepticism at some of the local lymph node data and call their attention to going back to the peer review report and looking at the accuracy of that data.

I wonder whether you would mind commenting on the similar evaluation that was presented for the guinea pig data by that report.

DR. MAIBACH: Was that heard by everybody? I'll comment. I was specifically asked to comment: If you go into the ICCVAM list of chemicals that are clearly defined as a plus in the columns -- I went over this this morning -- there are many of those materials that are probably not allergens. Because in guinea pig testing, you need very sophisticated laboratory directors and readers, but mainly the directors, to know how to separate irritation from allergen. Many of those are false positives.

Conversely, many materials that clearly produce allergen in man are negative in all of these assays. They are negative in the lymph node assay. They're negative in the guinea pig. And they're often negative in man. We don't have yet refined enough methods to deal with them.

So when people talk about sensitivity and specificity in an intellectual sense and a practical sense, they really have to go back and peer review each of the papers with the degree of confidence method that I mentioned which, unfortunately, was not done because of time restraints in that ICCVAM Panel.

DR. MEADE: I guess just then for clarity, would you agree based that on that panel report and what you're saying here, that the accuracy of the local lymph node assay is comparable to that of the guinea pig, for the data that's coming out.

DR. MAIBACH: I would say that as a general statement which the report said that the methods are comparable. But they give you different information.

Right now if I see a problem it's the fact that people don't quite understand how to interpret the data. I think one of the biggest problems we have in the false positives in the lymph node is so many irritants give us a positive. I would hate to lose all of those compounds to future human use if it's a false positive due to irritation.

DR. MEADE: Thank you.

DR. HEERINGA: Yes, Dr. Menne.

DR. MENNE: I enjoyed your talk, Howard. My question is not for you. It's for the wood industry.

I would like to ask the wood industry, you have plans or you must process this wood where you have plenty of workers exposed to dust and to the wood-containing chromate. And I would like to ask whether you have any epidemiological studies following such workplaces where you have incidences of sensitization or elicitation.

And then after that, I have a comment for the Fowler paper.

DR. HEERINGA: Dr. Youngren.

DR. YOUNGREN: This is Susan Youngren. I just want to answer that. Mr. Morgan will be addressing that as well as Dr. Joel Barnhard from Elements will both be discussing that later today. Can you wait until they're ready to respond to your question at that point?

DR. MENNE: Thank you very much.

DR. HEERINGA: Dr. Menne, did you have something specific for Dr. Maibach at this moment?

DR. MENNE: No, not for Howard. I had a comment on the Fowler paper here. It was getting around now. And --

DR. HEERINGA: Dr. Fowler will be speaking later as well.

DR. MENNE: Dr. Fowler will come

here?

DR. HEERINGA: Yes.

DR. MENNE: Thank you.

DR. HEERINGA: Excuse me. I'm sorry. Please go ahead. That's not the case.

DR. MENNE: I think it is a beautifully done paper. But I will say that I completely disagree with the conclusion. And I think it's a very controversial conclusion. The paper is a continuation of the Nethercott material. And what these good colleagues have been doing is they have made an immersion study, that is to say an open test, of the different chromium concentrations.

It's a hexavalent chromate, and it's a concentration around 20 ppm. And in these pre-sensitized individuals, they see reactions after two to three exposures. And what they see is that they see papules and redness. And they also take biopsies. And they have reactions particularly around the sweat ducts.

And the conclusion is that this is an irritation.

And I will say that I completely disagree with the conclusion, because this is what we are seeing when we are making open tests with chromate, nickel, and the other compounds also. And the explanation the irritation is that they have no control material.

Now you should keep in mind that they exposed the skin for two days or three days with 20 ppm of hexavalent chromate. Our usual patch test concentration under occlusion is 1,770 ppm. So this is very, very far from the diagnostic patch test level. And I think it would not have been unethical to include a control material. And I'm quite convinced -- I cannot say for certain.

But I'm convinced that a control material exposed to this very low concentration would have been negative. And I think the Fowler study is actually in good concordance with the David Basketter study which was mentioned this morning where they have reaction to hexavalent chromate in open testing of 5 to 10 ppm.

We have a preliminary study with a few patients also on dipping the hands where we had reactions also down to 10 ppm. Thank you.

DR. HEERINGA: Thank you, Dr. Menne.

Just for the record, the paper you're referring to is the Journal of Occupational Environmental Medicine, 41 No. 1.

DR. MENNE: Yes. I only mentioned this because it was handed out.

DR. HEERINGA: No. That's fine. It was distributed. That's fair. Dr. Maibach and Dr. Younger and others will have an opportunity to speak again. They are scheduled to speak again.

At this point, I have 12:30. If

there are any urgent questions that you'd like to ask of Dr. Maibach at this point. Otherwise, I'd like to suggest that we adjourn for lunch and then reconvene. Let's adjourn for a one-hour lunch and reconvene at 1:30.

Thank you very much.

[Lunch break taken at 12:30 p.m.
Session reconvened at 1:35 p.m.]

DR. HEERINGA: At this point in time, I'd like to call the Panel session back to order. We're going to continue with our public comments. Again, all representatives or individuals participating on behalf of the Forest Products Research Laboratory. And at this point in time, I'd like to invite Dr. Susan Youngren, who is with the ACTA group, to make her comments.

DR. YOUNGREN: Thank you very much.

One comment I would like to make is that the Panelist's will note that at the back of their document is a list of errors that we found in the background document. And we have provided either corrections or comments on that. That will, also, obviously be submitted to EPA.

DR. HEERINGA: This is at the back of your handout.

DR. YOUNGREN: At the back of our handout of the slides, you'll find a list of the comments.

For example, one of the comments that was made early by Jonathan and Tim was that the fact that they talked about the treated articles such as treated wood do not bear pesticide labels or other communication methods to warn the population of hazards. However, this is incorrect. Since 1998, CCA-treated wood has had a label that warns the population about the hazards of arsenic. So we wanted to make sure that you understand that the fact that it is a treated article, that it is wood, exactly like we're talking about with ACC-treated wood, it has been bearing a label.

I'd like to go over just briefly a couple comments and background on the MET and uncertainty levels. One thing about the MET, and we want to keep emphasizing this, that it is an elicitation threshold. We have seen documents that talk about the fact that possibly this could be used for induction.

We don't want to ever talk about that being used for induction or being used as synonymous in some way that it should be used as a protection method for induction because it is so much lower.

It is an elicitation threshold that elicits ACD in a hypersensitive population which is important, back to the statement that Mr. Aidala read, on the scope of protection that EPA is dealing with. That we are dealing with a very, very small amount of the population, that the MET is based on results from patch tests in humans, as obviously was described by Dr. Maibach, regarding the fact that it is already an identified, sensitized population, and that you're applying it for 48 hours with an occluded patch.

The 10 percent MET which was been described as an NOAEL for virtually all of the general population, or a no observed adverse effect level, because it protects the general population which is really where the concern that EPA has and 90 percent of the people that are known to the hypersensitive are already allergic. So you're obviously, depending on the prevalence rate, covering a large percent of the population from elicitation not just induction.

So the scope of protection is effected by the prevalence of sensitization in the general population. And you need to know that so you can look at the MET in the proper format. Additionally, a peer-review panel that was looking at an EPA document on how to do risk assessment for the Office of Water -- this is EPA Office of Water -- a peer-review panel described the 10 percent MET as analogous to an RFD.

For those of you who have dealt with RFDs, that's a reference doses. And reference doses always already have safety factors embedded in them. So that we've taken the 10 MET, said that it's analogous to an RFD with protection factors. That would be the level that you would be comparing to human exposure. And we want you to be aware of the fact that was a decision by a peer-review panel. What we all believe are competent scientists due to the fact that in many ways you are a peer-review panel as well, looking at this information.

Talking about uncertainty or safety factors and the four factors that were listed by Drs. Chen and McMahon, interspecies, intraspecies, product matrix, and exposure, we need to remind you that two of these are hazards factors that are really dealing with the toxicity issue. The intra- and interspecies, one is obviously dealing with the exposure portion if we're going to look at it from a risk assessment standpoint, obviously that's the exposure factor. And the product matrix, or sometimes also described as a vehicle matrix, can have a impact on both the hazard as well as the exposure. And you need to look at that when you're trying to determine whether or not you need to apply the factors or how you would apply the factors. And we'll go into more detail on that specific to ACC-treated wood a little bit later.

Keep in mind that we're saying that these factors need to be chemical specific and product-use specific. In other words, if I'm going to apply these to ACC-treated wood with chromium, it's going to be different than if I were going to apply this to something that was a chemical that was going to be used as a cleaner of floors. The exposures are different, the product use is different, obviously; and the chemicals are different. And you need to keep both of those in mind.

We also want to remind you that it is critical to evaluate the weight of evidence when determining the factor to use. You've got to look at all of the pieces when you put it together. And you need to evaluate the potential impacts of being overly conservative. Yes, we all want to protect. But we also need to make sure that we're not protecting to a degree that nothing is going to exist.

I'm going to try to summarize just the background that Howard and I went through which is almost an impossible task because who wants to follow up behind Dr. Maibach. But these are the jobs they give me. So what I would like to just mention and just a couple things.

One is that the LLNA may be appropriate for estimating induction thresholds. But we believe that it's much more validation is needed before it is applied to quantitative risk assessment. And we've actually given you some quotes exactly where that has been stated.

The MET may be appropriate for estimating elicitation thresholds, but we don't believe elicitation levels are appropriate for regulatory purposes. We don't believe that they should go farther than that.

And then we talked about the TRUE Test patches. And we actually have a picture for you. We actually brought some so you can see what they look like for any of you who have not dealt with a TRUE Test patch, haven't taken yourself in for one of those or have taken a child, to show that in clinical experience where applicable, in other words, where you actually have the data, we believe that these provide a lower bound on induction thresholds, a lower bound on active sensitization. And that safety factors are already incorporated when we're talking about these numbers. And we'll go into details how the numbers come out for chromium as we go along in our presentation.

I'd like to take this time now to turn it over to Mr. Denny Morgan. And he's going to talk to you a little bit about what we call the world of wood and the world of ACC.

DR. HEERINGA: Before you begin, Mr. Morgan, are there any questions for Dr. Younger from the Panel?

Oh, yes, Dr. Siegel.

DR. SIEGEL: Real quickly, can you expound on what you mean by lower bounds so we're all clear on that?

DR. YOUNGREN: Because the use of patch tests has been shown not to sensitize people, that if we're trying to determine what level is going to sensitize someone, that if you use the patch test and you don't sensitize people that's a lower bound on what induction level could be. In other words, it's not going to be higher than that number.

Does that make sense? Do you want me to try again?

DR. SIEGEL: Yes, please.

DR. YOUNGREN: In other words, if we know that the TRUE Test patch is used at a level of 20 -- I'm pulling a number out of the air here -- then we would know, and no one becomes sensitized using that, that 40 is not going to be an induction level.

Excuse me. That 10 is not going to be an induction level. I'm sorry. I went the wrong way. It's not going to be.

DR. SIEGEL: Yes.

DR. HEERINGA: Dr. Bailey.

DR. BAILEY: I thought in some situations -- is Dr. Maibach here?

DR. YOUNGREN: He is.

DR. MAIBACH: Yes, sir.

DR. BAILEY: Howard, sometimes in the diagnostic test patch kit it was my understanding that sometimes concentrations are exaggerated to bring forth an allergic reaction to certain substances. For instance, the isodiazlones, where we know that, let's say, 5 to 10 ppm, let's say, could be used, hypothetically, safely in maybe a shampoo product. If someone is experiencing an allergic reaction to isodiazlone, I believe the elicitation concentration is maybe 50 or 100 ppm?

DR. MAIBACH: Correct.

DR. BAILEY: Okay. But if you ran a sensitization study with that concentration, there's a high probability that it would induce the population with 100 ppm in a HIRPT, for instance. If you could comment on that. I did some work in there with you.

DR. MAIBACH: Briefly, Susan's point was that there is a phenomenon that we try to avoid in diagnostic testing where one single patch sensitizes. So in the past, we have before we understood what we understand today, we've had to lower concentrations on a number of occasions. So it's a balancing act. Too low, a single patch won't bring it out. Too high, we actively sensitize with a few materials. So I think that was her intent.

But the second part of your question that we don't know of active sensitization to either the .25 percent in petrolatum used in the United States, the TRUE Tests used in the United States, or the half percent INPEP used in Europe, or the TRUE Test used in Europe. They're both the same. Those TRUE Tests are the same.

But I don't know without looking into our data bases how many human Draize repeat insult patch tests have been done with the diagnostic patch test materials. I suspect some have been done, but it's not in my head. But as a general rule, we know that in the Draize repeat insult patch test, if we really want to get a positive to work backwards from, we have to increase the concentration of many of the materials we use. Neomycin, which we sell at a half a percent and at one time that sensitized many people, in order to pick that up in the Draize Test, we had to go up five- to ten-fold.

DR. HEERINGA: Thank you, Dr. Maibach. Any other questions?

DR. HAYES: Can you help me with the T.R.U.E Test? You indicate that the safety factors are already incorporated. Can you expand on that a little bit more?

DR. YOUNGREN: Well, again, it goes

from the fact that, if we are not inducing the population with that, that we already have enough safety factors incorporated because we're not doing what everyone has expressed concern about which is to induce additional people, in our case, with chromium sensitive.

DR. HAYES: So you've taken into account all these four safety factors or uncertainty factors that you've listed earlier in that test somehow.

DR. YOUNGREN: They have been because they have been done for so many years. We talk about interspecies versus intraspecies. Is that what you're asking me to go through each of those specifics?

DR. HAYES: The four of them, how do you eliminate them in the TRUE Test.

DR. YOUNGREN: I think you have from the standpoint.

DR. HAYES: I know you think you have. How had you done it.

DR. YOUNGREN: Well, obviously, I don't have to deal with intraspecies because I'm not going from animals to humans. We can talk about that. Intraspecies has been done for so many years, and we can talk about the fact that there are --

DR. HAYES: Intraspecies now?

DR. YOUNGREN: Intraspecies. So you and I are different. There's no question about that. Right?

How we're going to react is obviously a question. However, if the fact that we have 60,000 people in the United States that are tested every year with this test and we're not seeing additional sensitization coming from that, and that's every year using these; we believe that we have covered the intraindividual variability because of the numbers of people that have been tested and we can multiply that back a certain number of years.

From the standpoint of the product matrix, they've worked very hard to get a matrix that would deliver it without providing additional irritation. So a matrix that is simple, again, just looking at what the exposure to the chemical is. That's a product matrix.

From the standpoint of exposure, all we're trying to determine from this test is whether or not, based on the exposure that you have, you will become induced.

That's the question I'm asking. And I'm saying we will not. And that's how we have dealt with the four safety factors that they list, but they list them for being applied to the LLNA. They have not listed that those need to be applied. And, in fact, I would take and look at them slightly differently if I looked at just straight safety factors for other things, these safety factors that have been listed by others to be applied to an LLNA to get it.

No. Inter and intra, obviously, are ones that are normally used. But we can throw any in any variety of them. I've seen up to seven safety factors listed. And I have seen up to, you know, this is on other pesticides for systemic uses with a 10,000-fold safety factor required. Those are really hard to get to.

DR. HAYES: Thank you.

DR. YOUNGREN: Certainly.

DR. HEERINGA: Dr. Menne, Dr. Meade, and then Dr. Pleus.

DR. MENNE: You said that as industry you were more interested in induction than elicitation. And I think that's a very hard standard to cope with because you have actually many people sensitized in the population and Howard, for example, told us that many react to gold without having any skin disease.

And another example would be the poison ivy. If you know you have the poison ivy contactality, you will not go out in the forest where you have the plant and you will not have the disease. So what is actually costly for the individual in disease, disability, and what is costly for the society, is not the inductionality that the elicitationality. And I think when you have a chromate which is actually ubiquitous in our surrounding, I think it's of the utmost importance that you think in elicitation and not in induction.

DR. YOUNGREN: May I respond.

DR. HEERINGA: Yes, you may.

DR. YOUNGREN: The induction level being of importance was actually what has been stated to us by EPA as well in our discussions of what to do and how to deal with this for the fact that we're looking at the general population and not a hypersensitive population when you're trying to estimate how to set levels for that. And that's where that came from.

And I understand your concern. But we'll also be -- you know, I know others will be talking about the prevalence rate of chromium sensitive in this country. And we'll be talking about the fact that there is a very, very low prevalence rate. It's been stated as low as .08 percent. Which means that, if we're looking at that, we're already protecting 99.2 percent of the population without doing anything if we're looking at those that are being induced only above and beyond what's already there.

And I know that there are a variety of other numbers that have been listed for what the population is that is sensitized. But we're dealing with the published data at this point.

DR. HEERINGA: Dr. Menne, did you

have a follow-up?

DR. MENNE: Just to follow up. I think it's very difficult to quote this epidemiology because the data is weak. It is mainly extrapolation of data coming from patch testing of patients. And there's a few studies in Europe on background population epidemiology. There are some studies from San Francisco on nickel and neomycin. But there's no study on the general population epidemiology in the U.S. on chromate. It's not done.

DR. YOUNGREN: Thank you.

DR. HEERINGA: Dr. Meade has a question.

DR. MEADE: If you could clarify for me. I think I must have missed a point or misunderstood. Were you saying that, because you're not inducing people by testing them with the patch test, you think that you are at a safe level to protect for induction?

DR. YOUNGREN: That's correct.

DR. MEADE: How can you make that assumption when you're doing a one-time exposure as opposed to people that are getting repetitive exposures potentially at this dose level.

DR. YOUNGREN: For one thing, a certain number of these people are coming in not just on one time exposures. A lot of the people that are coming in with a rash are being already tested to determine whether or not they're going to get an additional rash. And so we believe with the level that we're at there we are going to be protecting people.

We can discuss whether or not you need to put additional safety factors on to go to lower levels, et cetera. That's where we are at this point.

DR. MEADE: Just to make sure that I'm clear. You state from that one patch, testing thousands of people possibly repeating it several times, you think you're protected from repetitive exposure?

DR. YOUNGREN: We can go into the specifics of the repetitive exposure that we believe people are going to get which was one that we don't believe that there are high levels, if any level, of Cr(VI) that they're going to be exposed to on the ACC-treated wood. And that the level chromium, if it's there, decreases over time and quite rapidly. And we have the data, and we presented the data to EPA showing that, that it decreases over time. So you have got to keep that in mind.

And, secondly, your repeated exposures, if you have any, are too much, much lower concentrations than anything that you would get in the patch test. And there's also that that has to be put into the picture when you're doing it which is all of those pieces that have to be put together on why we believe that level is protective.

DR. MEADE: Thank you.

DR. HEERINGA: Dr. Pleus and then Dr. Foulds.

DR. PLEUS: On Slide 3, you have a bullet point that says that 10 percent MET is analogous to an RFD.

DR. YOUNGREN: That was how it was described, yes.

DR. PLEUS: Can you just give me some details or expand upon that a little bit?

DR. YOUNGREN: The question was brought up to the peer-review panel for the Office of Water document on what they would do about things like dermal sensitization. And their reply was they would use a 10 percent MET, and they described that as analogous to an RFD.

When we went back, and in fact, I said it was equal to an RFD at one point. And I was corrected by the Office of Water that it wasn't equal to an RFD, that it was analogous to an RFD. I think that's maybe a questionable point.

Now, I will say that the Office of Water said that they have never pushed and used it. They've never done dermal sensitization as an issue with anything. So they haven't set standards based on dermal sensitization. That's what the peer review Panel described it as.

DR. PLEUS: Just a quick follow-up.

DR. HEERINGA: Certainly.

DR. PLEUS: I've been reading a lot of material for a lot of days, so excuse me. Did you go into detail in your report on this?

DR. YOUNGREN: I thought we had. Just a minute. Can I look real quick?

DR. PLEUS: You can look. And I'm sure I missed it, but if you can point that out for me.

DR. YOUNGREN: You may not have.

DR. HEERINGA: Dr. Youngren, maybe we can come back to that.

DR. YOUNGREN: That's fine.

DR. HEERINGA: We can let everyone know. Thank you.

DR. YOUNGREN: That would be fine.

DR. HEERINGA: Dr. Foulds.

DR. FOULDS: Just going back to the safety factors incorporated, you stated that about 60,000 TRUE Tests are performed in the U.S. each year I think is what you said.

DR. YOUNGREN: Yes, that's what we've been told.

DR. FOULDS: And that did not induce any active sensitization. Is that to all substances tested on the TRUE Tests or just Cr(IV).

DR. YOUNGREN: We're just talking about Cr(VI) in that case.

DR. FOULDS: And how have you ever attempted to measure whether there is any active sensitization or not from the TRUE Test? What follow-up studies have you ever done to actually investigate that?

DR. YOUNGREN: I have not personally done any follow-up studies. Howard?

DR. MAIBACH: The source of that quote, I'm not sure. So I'll tell you what I do know.

At the North American Contact Derm Group, we're very interested in active sensitization. We don't want to sensitize people. We've asked on a number of occasions are people getting the positive at 10 days, 2 weeks, 3 weeks. And the answer is that with the exception of paraphenaline diamine, it hasn't been reported yet.

DR. YOUNGREN: Can I just reply to Dr. Pleus's question?

DR. HEERINGA: Yes, absolutely.

DR. YOUNGREN: It's page 13, footnote 33.

DR. PLEUS: Thank you.

DR. HEERINGA: This is response to the question --

DR. YOUNGREN: This is in response to the question about the RFD and analogous to the RFD.

DR. MENNE: Just a short comment concerning the patch test and sensitization from patch. We have done general population patch testing in Copenhagen in an unselected populations. And we did it in '91 and repeated it in '98. And in these two studies, we had some who participated both in the first and second panel. And we didn't see any sensitization to chromate in this group of individuals. So we have done a proper study on these things.

DR. YOUNGREN: Thank you.

DR. HEERINGA: Thank you very much, Dr. Menne.

Any additional questions on this

one? Thank you very much for a stimulating discussion.

Mr. Morgan.

MR. MORGAN: My name is Dennis Morgan. I'm the general manager of Forest Products Research. And I want to thank you the Panel for meeting today. I want to thank Mr. Jones and Dr. McMahon and Dr. Chen for raising this issue several months ago. It allowed me to meet Dr. Maibach. And some of the lecture that you've heard today, I've sat through many of them over the last few months to become somewhat educated on this. And I feel much more informed on the issue.

Before I go into my presentation, I want to respond to Dr. Meade's question regarding the patch test and what we're talking about there.

If you go through the uncertainty factors as Dr. Chen laid out and we have a test to develop an NOAEL and then we have intraspecies variation of a factor of 10, what we're saying is, because this patch test is done over 60,000 people a year, the intraspecies or interindividual difference does not have to be 10 if you use the level of the patch test which is below where the LLNA and the other tests come out at. That's why we say it's a lower bound for the test.

The other two uncertainty factors that you talked about which can still be included. But as Dr. Youngren pointed out, we're separating in the uncertainty factors the difference between the hazard assessment and the use assessment. So at a certain point, and as you have seen the other presentations come together, the repeatability as you talked about is a use assessment which is different than the hazard assessment. And we're saying there's a point in there on the hazard assessment.

DR. MEADE: Thank you.

MR. MORGAN: Treated wood has been around for over 50 years using chrom both as ACC and CCA. It's been used in Europe. It's been used in the United States.

The points that I'm going to try to cover in this presentation are the dermal contact with wood preservatives, the hexavalent chromium and treated wood exposure data that we have, the practical exposure data considerations, and some risk model assumptions. I'm a little bit out of order because I kind of got through a couple of risk models assumptions in responding to that question.

Hexavalent chromium, Cr(VI), is a major ingredient in the two major wood preservation products in the worlds. That's CCA and ACC. CCA is still used in the United States. It's not used for consumer products. It's still used for commercial applications. Approximately one third of all the utility poles in this country are still CCA-treated.

ACC has been used extensively in Europe. It was one of the major products that when CCA was banned in certain countries in Europe, ACC was the substitute product that was adopted in Europe. ACC had some specialty uses in the United States that due to labeling issues, the current label holder has decided not to sell or are not being made.

About the middle of last year, they had very water cooling tower where it was chosen because of the very poor leachability of the chromium and copper out of the ACC-treated wood in comparison to leachability of arsenic coming out of the wood.

Why we put chrom chromium wood? It's not a preservative. It has virtually zero biological activity as a biocide in the wood. It's there to react with the organic material in the wood fiber to permanently fix the copper, or in the case of CCA, the copper and arsenic, to wood. It's primary purpose is a fixation agent.

We can go into the whole history of how this came about. But under a normal FIFRA deal back when this all started, I would probably not say it's a preservative. I would say it was an inert in there that was there as a binder. It's also used to dissolve the copper in the aqueous solution. One of the fortunate affects that it does is it does give a good corrosion inhibitor so treated wood material that's put together with metal screws and everything does not rapidly rust and you don't have decks or fences falling apart.

Not all exposures are the same. I think Dr. Youngren spoke to it. We talked about some other things. The risk assessment model that allowed the mouse LLNA data was originally started from was developed from cosmetics or personal care products, things that are intentionally put on the skin. You know, they can be applied generally to almost any part of the body. Anywhere your hand can reach, you can put upon a personal care product.

Wood preservatives are incidental contact with the skin. They are aren't intentionally applied to the skin. They're applied to the wood. As Dr. Chen explained, they were pressure-treated wood. And where the exposure comes from is surface residue. And for hexavalent chromium, it's the surface residue of unreacted chromium that is at the surface.

Primarily, the exposures that you would see in treated wood would be to the soles of the hands and shoes and clothing. Originally, when I came back here, I brought a couple samples like the TRUE Test, and I had a piece of wood I was going to show you. It's kind of hard to get it underneath your eye and everything. But it didn't make it through TSA screening for some reason.

I said that chromium on the wood is due to unfixed or unreacted chromium. Dr. Chen talked about the fixation process. That's a term of art that's used in the wood treatment industry. It's really the reduction of Cr(VI) to Cr(III) in the wood structure. The fixation reaction when it's complete -- I should say complete and the chemical equilibrium is a poor term. When it reaches a virtual point in the fixation in the wood industry, we have an arbitrary number. Where we say it's less than 15 ppm in the wood by a particular test we have, we say that's a complete fixation.

As a product reacts over time, the fixation goes down. I will tell you that this curve, the fixation curve, is a steep curve in the beginning. And it is very temperature dependent. At 70 degrees, it takes approximately four days to fix the wood. At

35 degrees, it can take six weeks.

It's a well developed known reaction. And the rate of fixation for CCA and ACC is the same. The significant difference is we start with at lot more chromium on a relative basis in an ACC-treated wood than we do with a CCA-treated wood. So, therefore, to get to the same endpoint, it takes a longer period of time.

Virtually every American is exposed to treated wood. We've been treating wood with hexavalent chrom since the 30s. Most of suburbia has decks, fence posts. As I said, about a third of the utility poles in this country are CCA-treated. It gets around quite a bit.

During that period of time, I guess I'm sort of responding to a question Dr. Menne asked. We don't know of any ACC problem linked to treated wood. We don't know of it in treating plants; we don't know of it in the use industry. I'm not going to say it isn't there because I haven't interviewed all the 270 million Americans. But it has not been a significant issue.

In the last 25 years, the use of treated wood was gone up tremendously in the United States, while the prevalence rate of chromium ACD has gone down at the same time.

SAP has met on treated wood a couple of previous times. In 2000, the EPA did not assess the dermal sensitization hexavalent chromium in CCA-treated wood. The EPA staff, if I read the documents right, asked dermal sensitization and whether it should be assessed. And the SAP Panel at that point in time instructed the staff to review what the State of New Jersey had done with chromium assessment values.

That Panel somewhat continued in 2003. Not the same SAP, but as part of the CCA that met again. And at that point in time, they again did not review the dermal sensitization for the revised assessment for CCA-treated wood. That's not to say there was an overt point like this particular meeting for people to look at. And they were looking at a lot of other things with CCA-treated wood. So it may have been overlooked.

We've reviewed the OSHA reports for the last 10 years. And we cannot find any data of reports of ACD cases specific to the exposure of hexavalent chromium involved in the production of chromium products. That's like at the manufacturing points where we make wood preservatives or where the chromic acid is made at.

Elementis is currently the major supplier in the world. And I believe they are the only manufacturer in the U.S. And they have no evidence of ACD reported in any of their production facilities. But I think Elementis will speak for themselves on that.

We also went back and searched the Bureau of Labor Statistics data base, and OSHA does not have reports of dermal issues related to the subgroup of wood treatment plants for a 10-year period 1993 through 2002.

There was also a conference on wood treatment plants in Germany a few weeks ago. And all the ACD and dermal sensitization was not the issue of the conference. There was a discussion of dermal issues at wood treatment plants. The members of the treating industry that there, did not report any ACD or dermal irritation at their plants.

Well, this has been kind of an unusual registration. And I think most of the people sitting at this side of the table will agree with me on that. When ACC came up, because the registration came up because it hadn't been used in the United States, there were a lot of discussions about it. Well, the EPA sent one of their senior staff members to

Europe to visit some treating plants and look at some production.

The report of that trip reported that there was no incidence of ACD in the treating plants or at the consumer use. And the staff member interviewed the people that she had met.

Again coming back to risks and toxicity, with ACD the induced sensitized person is the nonreversible side of that. The elicitation side, as pointed out, that is a reversible. That is the symptom that we see there. But ACD as far as the elicitation or what we see, is reversible and it is avoidable.

Some of the issues that have come up in the past just to bring you up to speed. EPA has determined that Cr(VI), at least for wood is not a cause of death. We don't have any acute poisoning deaths. It's not a cancer problem in treated wood. And it doesn't have any reproductive affects.

Again, sort of coming back to the uncertainty factors. The uncertainty factor protect against ACD should be based upon the nature of the endpoint. This is a reversible endpoint. This is not a reproductive. It's not an endocrine disrupter. The elicitation is reversible and avoidable affect.

You've seen some stuff that proposed a factor of 3,000. These are sort of the default factors in the uncertainty. It's the combination of the all the uncertainty factors being proposed by staff. And the total is 3,000. It's the maximum number in each group. I think that there were some comments by Dr. Griem that were discussed this morning where he talks about the interspecies uncertainty factor and how that should be Round 1 for his assessment of the chromium product.

We also got into the patch test which we'll hear again. But because of the size of that -- what we're saying in that is you can take the animal studies. But you have to look at them in terms of also the human data that's out there. And if applying the uncertainty factors takes you far below what we're currently doing with human folks, you have to examine that and take a look at that. We're saying that human data has to be a point on that.

The exposures, the combination of all these uncertainty factors are very tremendous given a lot of the other human data that is just beyond the LLNA data. A factor at 3,000 just blindly applied as a default factor coming in can eliminate a lot of chemicals. It will end up eliminating a lot of home-use pesticides. It will eliminate a lot of treated-wood products. And it would eliminate a lot of household products around if it's just blindly looked at from this one study.

I want to thank you for the time. And I will be happy to answer questions at this time.

DR. HEERINGA: Thank you very much, Mr. Morgan. Are there questions from the Panel? Dr. Meade.

DR. MEADE: In listening to what several of you have had to say, I'm beginning to question whether the issue is really not the use of the local lymph node assay, but the uncertainty factors that people have associated with it. Is that really the issue? It's not so much that the raw data, the EC3 value that is set by that assay is inappropriate.

Because if you look back at the data that's been presented and you just look at those factors, they get scaled way up because of the uncertainty factors applied. And from what you were just talking, is that really your concern?

MR. MORGAN: That's one of the major concerns that we're talking about in this. I think in the case specific which we'll kind of do another round robin, there are some other issues within the LLNA test that will bring to the forefront with the local lymph node assay.

DR. HEERINGA: Yes, Dr. Hayes.

DR. HAYES: I think it was one of your earlier slides. You made the statement, "The use of treated wood in decks has been increasing dramatically in the last 20 years while the prevalent of chromium sensitization has decreased." Do you have that data?

MR. MORGAN: Which data?

DR. HAYES: Either that it's gone up for the wood usage and that the prevalence has gone down.

MR. MORGAN: Do I have it here to present to you? No, I don't; but I can get it to you. The data, we based upon the sales of the underlying chemicals that are reported and the increase in the usage. Chromium is -- the only preservative used for chromium is in treated wood.

DR. HAYES: You've got that data. What about the prevalence data?

MR. MORGAN: Well, there will be a later speaker who will speak to the prevalence. But there are some studies by the North American Dermatological, Howard's group, that reports the prevalence rates every 15 years.

DR. HAYES: That's a pretty strong statement. And there's no data that I've seen to support it.

MR. MORGAN: That will be presented later this afternoon or tomorrow.

DR. HAYES: Thank you.

DR. CHU: I have two questions. These are exposure-related. The first question is: Are you aware of any study data to indicate that to what extent, say, schoolchildren are exposed to chromium when they are at play in the playsets that are built of pressure-treated wood? That's the first question.

And the second question is: Why do you contend that, from the pressure-treated wood there is a minimum of transferring from the pressure-treated wood of chromium to a person's skin? What if this chromium-treated wood has been cut in a factory where the workers saw the wood, where the sawdust flies in the air, or attached on the skin? Are there any studies to indicate that the release of chromium there is a minimum because these are all considerations when a regulator tries to set a standard to protect the workers as well as the public.

MR. MORGAN: I'll restate your questions, and try to answer them. The first question is: Is there any data to identify the exposure to children to treated wood?

DR. CHU: Yes.

MR. MORGAN: There is quite a bit of data on that. If the question is: Is there any data specific to ACC-treated wood? The answer is no. There is a great deal of data for CCA-treated wood. And what we're talking about is the exact same use pattern. And so a 2 by 6 that's put into a deck or used as a fence post, the children are going to have the same exposure to that wood as they would to CCA-treated wood.

The difference that I think, as Mr. Jones alluded to earlier, is the actual surface residue between the different treatments may be different. That's a separate component of the overall issue.

Now, is your question: Do we have surface residue data for ACC-treated wood?

DR. CHU: Yes.

MR. MORGAN: I'm glad I got that point. I think that Dr. Layton, Dr. Dang, and several of us are discussing the appropriate protocol to develop that data to EPA's satisfaction.

DR. CHU: Yes. Part 2 of the question.

MR. MORGAN: Part 2 of the question is on cutting the wood and the exposure. In cutting the wood, you're going to expose a fresh surface area. But the reaction rate is not different in the interior of the wood as it is on the surface of the wood. In fact, it's generally quicker within the interior of the wood because the chromium reacts with the organic fibers. So you don't have the artificial limit of no organics that the air would interface. So within the wood, it gets to the cell structure. And it will react on the surface of that cell structure and reduce from Cr(VI) to Cr(III).

The second part of that was the dust issue that is involved with that and the creation of sawdust and everything. I believe that's the issue.

That is sort of a two-fold question. One is where it's done in another factory and everything, there are precautionary measures that are handled in almost all wood-cutting issues in the United States where wood, treated or untreated, is and the saw dust is generated in a commercial sense. So the other issue -- you also have an issue of had long after treatment does the decay take place.

The longer you are away from treatment, the more the Cr(IV) is reacted to Cr(III). So you have Cr(III) in the wood rather than Cr(IV). If it's 70 degrees Fahrenheit and you're 10 days after treatment, you aren't going to find any Cr(VI). If you're 40 degrees, you may be six weeks.

DR. HEERINGA: Dr. Chu, any follow-up?

DR. CHU: Earlier this morning we

heard from Dr. Menne the issue is not just as it relates to chrom, hexavalent chromium. And, in fact, there is some data suggesting that trivalent chromium may well be also the culprit, too. The reason that it's not indicated here because of the absorption.

Now that you have a situation potentially that the trivalent chromium exposed to either the general public or the workers, how do you address that, the safety issues? Yeah.

MR. MORGAN: Well, I think if you're talking about the specifics that are in the Hansen paper that came up as part of the study, we have to look at a lot different issues involved with that. And I'm going to give you an engineer's approach to this, not necessarily a toxicologist's approach.

First of all, as I read that particular study, you had a water soluble chromium system. The trivalent chromium that is a result of the reduction in ACC-treated wood from Cr(VI) to Cr(III) is generally water insoluble. So they test for two different species of wood. I think that the issue is whether chromium chloride is analogous to whatever chromium complex we end up with in the treated wood.

The other issue that's related to that is whether from ACC-treated wood or CCA-treated wood. CCA-treated wood has a lot of wipe studies that were generated for the risk assessment task force so that we have some idea of what the trivalent amount of chromium is at the end of the fixation process.

When we talk about hexavalent chromium, we have a certain time frame after processing where we're going from hexavalent to trivalent. And after that, we're talking nothing but trivalent. I think that in my discussions with the gentleman to my right, the trivalent has not been a significant issue because they looked at it -- my believe belief is they look at it -- with the CCA.

DR. CHU: Thank you.

DR. HEERINGA: Dr. Morgan, I have a question. You have pointed to the European use of ACC applications in treated wood. Two questions: What portion of the market share does ACC represent in terms of treated wood use in Europe? And is treated wood used in decks and walks and other things as extensive there as it is here in the States?

MR. MORGAN: The answer to the second question is, no, not nearly as much. And to somewhat put it in relative terms, my understanding is about 70-plus percent of all the treated wood is the North American market. And the rest of the other 30 percent is spread through the rest of the world.

In Europe, depending upon what country you are in, the ACC can range of up the 50 percent of the treated wood in the country and to zero in some other countries because of the different regulations. My market survey puts the number about 35 percent of all the wood through Europe.

DR. HEERINGA: Thank you.

Any other questions for Mr. Morgan from the Panel? Dr. Chen.

DR. CHEN: I think I need to make some clarification. One thing that we discussed earlier in the morning, when we use a human sensitized population in the uncertainty factor, we are at that time because they are using the sensitized population. So we are using the uncertainty factor of 3. It's not 10. It is reduced to 3.

The second thing that I need to clarify is that, for the newly treated, wood fixation state is not complete and both of the chromium is in the Cr(VI). In general, that we believe that the Cr(VI) is much more potent when we talk about sensitization.

And once a fixation step is complete, basically it staying in the Cr(III). So when we see the newly increase of use of the treated wood, not necessary means the increase chance of the exposure to the Cr(VI). And the Cr(VI) and Cr(III) become an major important. We need to differentiate between these two.

And the third thing that we need to mention is that, in the chromium when we see those kind of patch tests and those kinds of things, we do have one concern that those people that are going to have both those patch tests, usually they are kind of going to the dermatologist for some kind of health concern.

But in general, that general public most of the time they're exposed to Cr(III) not really Cr(VI). So in this case, it's possible that the general public may not have the chance to be induced for Cr(VI). So this does have this kind of concern. So I just needed to point this out.

DR. HEERINGA: Thank you for those three points. Any questions? Mr. Morgan.

MR. MORGAN: May I respond?

DR. HEERINGA: Sure. Absolutely.

MR. MORGAN: When Dr. Chen talked about the factor of 3 in the Nethercott study, we're kind of talking at two different issues. It's what the study is and what's going forward. What we're basically saying is that on the interspecies, if you test 60,000 people every year, the uncertain on 60,000 people should be 1 is what we would propose.

In the sensitized population that Dr. Chen addressed or in the addressment of that study, the Nethercott study, they used a factor of 3 with a population of 54 as the test subjects.

DR. HEERINGA: I'm sure Dr. Maibach

mentioned it this morning. But what is the dose in the TRUE Test patch?

MR. MORGAN: Eight ug/cm2.

DR. HEERINGA: I do recall that now. Thank you.

Any additional questions from the Panel?

I think we'll continue with our sequence of presentations. Dr. Maibach, are you up?

DR. MAIBACH: Yes, sir.

This will be brief; I'm sure you'll be delighted.

I was asked to comment on the patient's referred to the University of California San Francisco Environmental Dermatosis Clinic. The clinic started in the 60s. It still goes. Patients can be referred by any health care worker. And they're usually referred with an undiagnosed eczematous eruption or a diagnosed eczematous eruption that's not getting better in which the health care worker or the patient says, well, maybe I'm allergic to something such as the treatment.

And we, of course, because of Bonneviv in Denmark in the 1930s, we have used chromate as has everybody else for almost all of these patients. When we started in the 60s, we had a screening panel of about two dozen. Now we have a bare minimum of about 65. And if it's an occupational patient or a woman or a man who has a dermatitis on their face, it might be 100 or a 120 separate chemicals under this wall aluminum chamber.

In the patients who are at chromate issue -- we have two types. One type which used to be not uncommon were cement workers. At one time in California, up to maybe 10 to 15 years ago, these people worked the way I did as a high school student. I spent a summer in this job. And my body was immersed on these hot days in mixing cement and it was all over me.

Some of these people, these professional cement masons, they've been studied in two Ph.D. theses, one in Norway and one in Denmark. They were often sent because their dermatologist knew they were cement masons and they had a hand dermatitis. So that's one population.

That has vastly decreased in our catchment which is Southern Oregon, Nevada, and California for the most part. We still see, now that the dermatologist are less familiar with cement eczema, we still see the occasional patient with cement that we realize, we take the history and put two and two together and test them. So even now in 2004, we still see the occasional one.

But it's really disappearing. Not because we've added ferrous sulfate the way it's been added in certain countries in

Europe, but just because of the changing work practices. The cement is delivered in big trucks. It's a much cleaner occupation.

But we still see patients as you will see in the patch test data who are chromate positive. I mentioned this morning that it's one of those materials that, if the history doesn't fit, we often repeat it to see if it was just a marginal irritant and hence would not be repeatable as a single patch or if it was excited skin and, again, would not be repeatable.

After the cement masons, we see several patients a year who seem to fit a clinical syndrome. They really do seem to be allergic to the chromate leached from the leather shoes. Once we make the diagnosis, the outlook or prognosis is fairly good. We put them in substitute shoes for six months, nine months. Many of them can go back to regular shoes. Some of them continue to wear the substitutes for long periods of time.

In the past, and by that I mean greater than a decade ago, certain paints had for functional purpose chromate added. And we were looking for those patients because we were thrilled when we found one when we would really make an intervention. They obviously became painters without chromate. We haven't seen one of those in a decade.

We used to have a certain small chromium plating industry in our catchment. We don't see those anymore. That's obviously done in some other part of the United States or the world. Our last primer chromate patient was again over a decade ago. I think the industry practices have changed.

Now, when you take the ones that we can explain, the rest go into the category of gold. They are a mystery. We believe if it's repeatable, that they probably do have cell-mediated immunity. They do have delayed sensitivity. But we cannot find a cause and effect relationship. We cannot define a disease. But one of your next speakers is going to help us find hidden sources of chromate. Maybe we'll be able to explain it after your presentation.

Now as I said, the explanation when you look at that statistics from centers that don't have the time and the leisure to go into the depth that we do, one is: Is the patch test positive without a relevant history, just simply excited skin. Cytokines going around the blood stream. When they decrease, the positive patch will not be repeatable.

Do they have an irritant response? Now, it's quite interesting that a really interesting thing to me at least is that the patients, the 50 percent that we can not find a disease to go with the patch test, all of those almost by definition are able to wear leather-chromated shoes.

So in summary, I would simply say that chromate has been studied energetically for decades, but new things are being learned all the time. The work that you referred to is the Hansen study from Dr. Menne's laboratory and department was a revelation. We somehow missed the significance of trivalent chromium before. I suspect there are many things that you can instruct, you can help in policy with our colleagues and governments all over the world that will answer many other questions in the years to come.

Thank you.

DR. HEERINGA: Thank you very much, Dr. Maibach.

Are there any questions in response to Dr. Maibach's presentation?

DR. ISOM: I was wondering on those 50 percent that you said you cannot explain, is there an age distribution or is that just general population?

DR. MAIBACH: There is undoubtedly an age distribution. I don't know it. But I suspect that Torkil Menne does or Iain Foulds does. Do any of you know the unexplained? Is there anything unusual about their age distribution?

DR. FOULDS: Not that I'm aware of, no. I'm just a little bit concerned about the high rate of unexplained rate. Often it's said that unexplained reaction is sort of a reflection of your own knowledge.

DR. MAIBACH: Fortunately, I am aware of that.

DR. FOULDS: I wouldn't like to imply that as far as you're concerned, Howard. I feel that most of my positives are relevant, that I can usually find a reason for them. I was interested that it was as high as 50 percent here.

DR. HEERINGA: Any other questions

or comments? Okay. Seeing none, let's move on to our next element in this presentation. Dr. Youngren.

DR. YOUNGREN: I'm the last element in this presentation so you guys can all get ready to breathe a sigh of relief.

And, Dr. Foulds, I'm glad that you are brave enough to say those things about Dr. Maibach.

DR. FOULDS: He's going to hate me now.

DR. YOUNGREN: I'd like to talk specifically about the Cr(VI) assessment because, obviously, that's our concern.

The most frequently referenced and relied upon study for establishing a MET for Cr(VI) has been the Nethercott et al. study that was done in 1994. And you're going to get a lot of details a little bit later from another speaker. But this is where they took 102 chromium sensitive volunteers, ran them through a first set of the study, decided that 54 met a very strict sensitization criteria, and then they recorded the positive responses over a dose response set of different doses.

There was one in 54 subjects who responded to the lowest Cr(VI) exposure. And, in fact, that person was further tested because it was such a surprise to get them at that that they discovered that they basically would react to anything including taking a shower. So they were obviously a very sensitive person to not just chromium but to everything. So you wonder really whether or not there was a true reaction or if they were just an anomaly in some ways.

The result for the 10 percent MET is the .089 ug/cm2. And Dr. Chen mentioned this in his presentation. The 10 percent MET has also been looked at for other studies. And Scott and Proctor in their document of 1997 did a benchmark dose model and looked at a variety of other studies that had been done and came up with a range of different MET values, 10 percent MET values, based on the fact that they were also done for different things. You've got dichromate acid. You've got it being done in a neutral solution. Chromic acid in an alkaline solution. And as you can see, the numbers range. In this case, they range from .55 to 12.50 ug/cm2. And keep in mind, this is in comparison to the value of .089 that was found in the Nethercott study.

Dr. Boukhman and Maibach in 2001 took all of this data, and they did a statistical analysis of these studies with running both a log probit model and a truncated log normal model. In putting all of this data together, again, we have been emphasizing all the way through here, looking at the weight of the evidence, they came up with a 10 percent MET of 0.72 of chromium per cm2 of skin. Again, this is for all the data.

And we believe that you should be looking at the weight of the evidence and putting all of the data together.

We'd like to talk briefly about the LLNA and be being specific for Cr(VI). This is another error that we found in EPA's background document which was sent to the Panel. In the background, they stated that LLNA study for Cr(VI) in Kimber et al. was done in acetone and olive oil. It was not. It was conducted with DMSO. And for those of you -- I had to learn these things -- DMSO enhances skin penetration and is also thought to be a strong irritant. And, obviously, it could affect the values you would get.

We believe that if you're going to assess treated wood, you need to use an LLNA study that would be conducted with water because that would simulate our exposures, because sweat which basically is how you would be getting the Cr(VI) or maybe a little bit of water if that might be the naked baby sitting on it. But with mainly about sweat, putting your hand down, sweaty, the Cr(VI) then going onto your hand. So we want to look specifically at that.

And there actually have been a couple studies that have been done, Ryan in 2002, used water as a vehicle and ran the LLNA and the EC3 at 44 ug for Cr(VI) cm2 determine that it wasn't a sensitizer. So if we ran the vehicle, which is comparable to the expose, Cr(VI) is no longer a sensitizer. Which then questions the fact of whether it would be a sensitizer in the type of exposure that we would be having.

Ryan also ran a 1 percent L92 which is a surfactant. He was trying to find something to use as an aqueous solution. However, there is a question of whether or not that in itself is causing some irritation. And so whether or not the LLNA values that you're seeing here, the EC3 of 15, also may have been actually irritation rather than sensitization. We can't answer that question, obviously. We might be able to go back to Dr. Ryan and see whether he has got his data and be willing to go through that. But at this point, I can't go there. I'm just hypothesizing here.

All of this compares to Dr. Kimber's results that were mentioned in the background which was from a 1995 report which was done in DMSO which is a strong irritant where you got an EC3 of 10.

If you look at all of this data and I just presented here to show that we did go through all of this, and then we went ahead and graphed it. And you find some interesting things on this graph. The top line is the Kimber DMSO set of data. The blue line is the 1 percent L92. The blue line is just EC3 -- excuse me. The red line, just so you can see it, so it jumps out at you, is to see where you are trying to cross this number. And then the water numbers, keep in mind, that we still didn't find anything at 44 micrograms of Cr(IV) cm2. That was the highest that was tested. They stopped at that point.

And you'll note a couple of interesting things. One of them particularly with the 1 percent L92 is the fact that we get this leveling off effect as you go on. And so then the question does come up as whether or not there was some irritation that was going on rather than sensation. And a question of why doesn't it continue to go up because you would expect it to.

It's also important to keep in mind that the EC3 or SI3 is a value that ICVAAM has decided was the point of departure, shall we say, that this is where you determine it. But it's interesting that it's not until you get to 22 micrograms that you start really seeing things above that as you're looking at it. So you have got all of those.

Also if you want to compare sort of what the ratio is between water and L92 or water and the DMSO, keep in mind you have got to compare down there where water is. So you're comparing the 44 down to about 14. You're not comparing zero to whatever the number came. And we'll bring that up in a few minutes.

Uncertainty factors. This is specific to LLNA. This isn't specific to anything else. This is talking about where we'd apply them. EPA has set a value of 3 for interspecies, a value of 10 for intraspecies. But they applied a matrix or vehicle EPA value for 10. We disagree with that mainly because of the Cr(VI) testing that was done in DMSO which was shown to be at least 30-times higher than with water. And water is the appropriate vehicle for this actual use. So we actually would propose a uncertainty factor of less than 1.

I know there's probably some snickers going on like, yeah, you got to be kidding, a .5? But, obviously, 1 would be fine.

Secondly, when we go down to the exposure, and this has come up already in one discussion, which is that EPA has a value of 10. And I realize that these numbers that I'm giving this, 3, 10, 10, and 10, are the numbers that were in the background document. But I think they've changed slightly. And I'm not sure if they're going to keep changing. Some of them, I know, got changed based on the comments that came in from Dr. Griem.

But we don't believe that the repeated dermal exposure is going to increase your uncertainty because the repeated dermal exposure, again, as I said before, if it occurs to any Cr(VI) and some of that is based on when the wood gets into the system and then when you would actually be exposed to it, is decreasing amounts of chromium over that time.

One of the issues that has come up is obviously what is a level that you're going to be exposed to. We do know from the standpoint of testing fixation that it does take some time particularly temperature dependent. However, we also believe that if you make wood, treat wood when it's really cold out, you're probably not going to be building with it very quickly either.

In other words, if I'm going to treat wood when it's cold in Minnesota, I'm probably not going to build a deck with it when it's quite that cold either because you can't dig footings. I've lived up north. And so you got to keep that in mind when you're talking about really how the exposure is going to occur and when you're going to actually have exposure versus wood moves very quickly through the system when it's warm. For anything trying to get a deck built right now, you're probably looking at a month or to two out before you can get someone to come out and give you an estimate.

The wood move very quickly from the wood treater to Home Depot, Lowes, wherever your local lumber mill is, lumber seller, to you to the consumer or to the person building the deck if NIOSH is concerned about the worker. But again it's fixing very quickly at that point as well. So we believe and we know that the Cr(VI) continues to decrease to the point where there is no Cr(VI).

And as Mr. Morgan said, we're finishing working through a protocol so that we can get the wipe sample data that will be comparable to the wipe samples that were done with CCA-treated wood.

And the same thing with what the transfer factors are, that is in the works.

We don't believe that we will see anything different than what we have seen with CCA-treated wood with fixation being complete when we're at the same point in fixation.

There have been multiple assessments of chrom dermal toxicity as well as chromium assessments. And I just want to go through a couple things because we think they are important for you to keep in mind when we're talking about dermal sensitization.

USEPA's Integrated Risk Information System, or IRIS, has always been sort of the gold standard for what toxicity is within the Agency. And they report on dermal sensitization for Cr(VI). And the IRIS document on Cr(VI) was updated in 2003. And they state that, "The concentrations of hexavalent chromium in environmental media that are protective of carcinogenic and noncarcinogenic effects are likely to be lower than the concentrations required to cause induction of allergic contact dermatitis."

They say, "Because the dermal irritation and dermal sensitization are the primary concern through the dermal exposure route, no further detailed assessment is necessary because any concerns are dealt with through an assessment of cancer and noncancer endpoints."

In looking at what was done with CCA-treated wood, we believe that following it through the cancer and noncancer endpoints, there obviously would be no concern. And we also believe that the levels when we look back and we can back calculate what those, quote unquote, "acceptable" levels would be based on playing on your deck and looking at systemic effects or carcinogenic effects which really doesn't come from the dermal issue; but the systemic affects for ingestion or dermal exposure that they would be protective for causing induction of allergic contact dermatitis.

The Office of Solid Waste, or OSWER, who spoke earlier today, also have reported and also have in their documentation that they also depend solely on this IRIS assessment. They state that IRIS remains in the first tier of the recommended hierarchy as a generally preferred source of human health toxicity values. Interestingly, it remains in the first tier. It's the only one in the first tier of the recommended hierarchy.

And the majority of contaminated site soil cleanup levels are based on potential soil ingestion rather than dermal exposure. We looked at a variety of ones where the information was out there to the general public of clean-up levels and how they had been established. And we were aware that they're not based on, in most cases, on dermal exposure.

However, we want to question the

fact that people do contact the soil. They sit on the soil, play on the soil. And yet as far as we can find, there have been no reports of ACD from this contact which would question the fact in many cases the levels are thousands of times higher than they would be if we were to go and pick one of the numbers proposed. In fact, it's probably a million times higher than the number that's been proposed by the Office of Pesticide Programs. And I really wonder whether or not we really need to go to that extent.

The SHEDS assessment for those of you who weren't involved with the 2001 and 2003 assessments of CCA-treated wood, SHEDS is a model that was created and modified to look at exposure for wood playsets and decks to assess the risk from both arsenic but also chromium to children exposed. And the adequacy of the exposure parameters that were used in the SHEDS assessment were looked at by two separate SAP panels.

The SHEDS model uses tox endpoints other than dermal sensitization. This follows the recommendation that is in IRIS. And as we said earlier, Mr. Morgan mentioned, that when the SAP was asked in 2001 what they should do, you know, what EPA should do, they were told to go back and look at the New Jersey assessment for how they set their clean-up levels for chromium. And in the 2003 assessment, the dermal sensitization was again not specifically addressed.

We have been told that it wasn't addressed because they felt that all the numbers that they had gotten off of CCA-treated wood were at such levels that they weren't of concern. But, again, they weren't numerically or quantitatively assessed. Actually, it wasn't even mentioned.

They did assess chromium dermal exposure. And when you run those numbers from the standpoint of systemic effects -- and those are out there on the internet. Any of us can run them -- there is no cause for concern based on systemic effects which would go back to the IRIS methodology that says that those levels would then be acceptable.

EPA has just recently come out in February of this year with an occupational risk characterization for exposure to CCA-treated wood. And they state that, "This report assesses exposes and risk to the potential receptors associated with exposure to arsenic and Cr(VI)."

They have said, "To address the concern for potential skin irritation and allergic potential for Cr(VI) from occupational exposure and in accordance with OPP policy, it was concluded that precautionary label statements should be included on the CCA wood preservative treatment solutions used in pressure treatment facilities."

To cover what you were questioning regarding the NIOSH question, this is EPA's method to deal with dermal sensation.

Interestingly, though, if you go on, the document notes that, "Endpoints selected for use in the CCA occupational risk assessment as a result of the October 2000 meeting, do not include dermal exposure."

And we want to understand why would we think that dermal exposure and dermal sensitization is important to a child playing on a playset or sitting on a deck. It is as important as of a couple months ago for a worker. We don't understand how OPP's policy can be one way for one thing and one way for another. We personally agree with their policy that they have here that we don't need to go as far as they've done with dermal sensitization that they're proposing now.

This is a discussion that we have

had over time. And here's a slide for us on the use of patch test for active sensation. And we know based on sales and other information, that 60,000 people are being tested every year in the U.S and they're not being sensitized. We can run through all kinds of numbers here on the fact that there are 293 million people in the country and there are 9 million visits to the dermatologist. Now that's not 9 million people visiting the dermatologist. But that's how many happened.

It seems dermatologists are doing very well here. And that there are 60,000 tests conducted or .02 percent. The initial positive for Cr(VI) shows between 1.8 and 9 percent positives. But only about half of those are positive on follow-up tests which leads us to do the math all the way out to find that 99.999 percent are not Cr(VI) sensitive.

I would like to show you some of the numbers that have come up in this discussion and it answers that, obviously, came up earlier, which is what is the concentration of the TRUE Test patch. And it's 8 micrograms of chromium per cm2. And this is based on .23 percent in a gel on paper. And we actually went through that calculation versus a patch test which was done in a Finn Chamber which is 0.5 pet petrolatum or Vaseline for those of us who are not quite as sophisticated. And that comes up with basically the same number of 7, 8 micrograms.

The LLNA from DMSO that Kimber did had a level of 10. In 1 percent L92, it was 15. Kligman 1966 was cited in Schneider & Akkan in 2003. And this was extrapolated by Schneider & Akkan to come out to be a level of 111. There were multiple sources cited in the LLNA in Schneider & Akkan in 2003 to come up with a level LLNA of 116. And then again with water from the Ryan 2000, we don't get it as a sensitizer at 44 micrograms of chromium per centimeter squared.

There's a range here, but it's quite a range from, you know, 7 to 116 or even possibly higher since we don't know what happens with water at 44. And we'd like you to just contrast this with a number that has been suggested by EPA at 1.0018 micrograms of Cr(VI) per centimeter squared as a level that we should use a level of concern.

I'm going to summarize. And I don't have the numbers in here, so I'm safe. We do believe that LLNA is for induction only. We don't believe that it has been validated for use in quantitative assessment. And including the author and one of the prime people behind the LLNA has said that we also want to make sure that we state that it cannot be used for evaluating thresholds for elicitation because we have seen that posed by some people.

The MET is for elicitation only. And we want to remind you that there is a large amount of information that is available for clinical experiences with Cr(VI). And we believe that when you're evaluating chromium, Cr(VI) particularly, and ACC-treated wood, you need to look at the weight of the evidence and the wealth of the evidence as a number of the reports state.

The reports on LLNA state you must look at it, and, in fact, human data is the best data that should be used and should be used first before any of these other tests.

From the standpoint of the case study, we believe that EPA's assessment is overly conservative. Estimated levels of Cr(VI) from exposure to ACC-treated wood are significantly lower than the levels used in clinical tests which don't result in sensitizing people. And we believe that exposure to ACC-treated wood will not increase the number of chromium sensitive individuals in the general population.

I'd like to take this opportunity to thank everyone for allowing us to come and speak and to lay out our concerns regarding the assessment that has been presented by EPA. And we will be glad to answer any questions. If there are any additional references, please, let us know. Thank you.

DR. HEERINGA: Thank you very much Dr. Youngren. Are there any questions? Dr. Hayes.

DR. HAYES: On your last slide before your summary.

DR. YOUNGREN: Yes.

DR. HAYES: My recollection in reading most of these articles that there wasn't much in them to indicate any analyticals as to the amounts present.

DR. YOUNGREN: The amounts.

DR. HAYES: These ug/cm2. In most

the articles, it didn't say that they did analytical to actually determine that's what was there. They dilute it to that or they accepted it as the value.

Do you have any insight into that? How good are these numbers?

DR. YOUNGREN: Which set of numbers? I know that the TRUE Test and the patch test numbers have been checked very accurately.

DR. HAYES: Have they gone back, and they've checked them even after shelf life; and it's still the number?

DR. YOUNGREN: Yes. Because are very much of an advocate about the fact that those are exact numbers. And if, in fact, you go on there, for example, those who sell the T.R.U.E Tests, the allergen patch tests that we have some here, you go onto their web site, they give quite specific details about their testing.

DR. HEERINGA: Dr. Maibach.

DR. YOUNGREN: Do you want to respond to the LLNA at all?

DR. MAIBACH: The TRUE Test was approved by the biologics division of the Agency. And, intermittently, they have provided that analytic data, and it is a very stable system.

DR. HAYES: That is really the only one that we know for sure that these analytics are what they say they are?

DR. MAIBACH: About 15 years ago, another system in petrolatum was approved by the dermatologic division of the Agency. And those numbers, as I recall, were not quite as stable but were within an 80 percent margin.

DR. MENNE: I just wonder whether your second to the last picture where you're making a comparison of active sensitization data and experimental data, if there's a little mix up of different things. Because we have a mix up of two systems. The one system is a diagnostic test system is designed in a way so that we can apply it maybe once in a lifetime or twice in a lifetime on patients. And the intention is that it should not be sensitizing. So we have intentionally selected a concentration that is not sensitizing and this is not irritating.

The LLNA are using doses which are intended to illustrate a hazard for a chemical when you come in contact with consumers. And that is to say it's also taking into consideration that such exposure might be repeated maybe daily or lifetime. So I think it's a very -- it's maybe a little misleading to put them up side by side. Because one test is for illustrating a hazard by a lifetime exposure, and the other one is a diagnostic test to illustrate whether an individual is sensitized and it's used once in a lifetime.

Thank you.

DR. HEERINGA: Yes, Mr. Morgan.

MR. MORGAN: I understand the difference that you're driving at. We did this for illustrative purposes. And, again, I think Dr. Meade picked up on this point. It is the application of uncertainty factors.

As you said, the sensitization deal is a once in a lifetime. And it's at a level that you want to make sure you want to sensitize it. As you've described the LLNA, it's for daily use going on. If you look at the first four numbers on the slide, they are fairly close together. The LLNA gives us numbers between 10 and 15. The diagnostic is between 7 and 8.

We aren't saying that they aren't there. We're talking about the level of uncertainty factors that have been applied to the analysis. Repeatability is a separate issue. I think this goes more to direct intraindividual intraspecies uncertainty factor that's been applied when we test 60,000 people a year and we don't sensitize them.

DR. MENNE: I still think it's a good idea to put them up side by side. It's very different things.

DR. YOUNGREN: I understand what you're saying.

DR. MEADE: I'd just like to comment on your suggestion that to be more appropriate the LLNA should have been run using water as a vehicle. And I guess I would ask you whether you would expect if dermatologists -- and I'll ask the dermatologists -- ran an open epicutaneous test in place of a patch test and just dropped water on the back of an individual containing the compound whether they would expect to see a response.

Water is not an appropriate vehicle for the local lymph node assay. It is nonoccluded. There is another than the surfactant abilities of the vehicle or the fact that the vehicle evaporates and leaves the material on the skin that keeps that test article against the skin. If you're proposing to run it in water, you really should propose not to run it at all because it would be an invalid test.

And in making the comparison between water and L92 and DMSO and suggesting that possibly it's the irritant effect of either L92, the surfactant or DMSO, that, again, is the purpose of the control. There is no more DMSO in the high dose of chromium than there is in the vehicle which is DMSO. So you're controlling for the irritant effect of DMSO.

The DMSO or the L92 may play some role in initiating those factors in the skin causing cytokine release; and, therefore, affecting Langerhans cell migration. But simply the irritant effect that you get false positives in the local lymph node with potent irritant compounds that you are testing is a very different effect than what you were proposing here for the vehicles.

DR. YOUNGREN: Do you want to respond as a dermatologist to the comment?

DR. HEERINGA: Dr. Maibach.

DR. MAIBACH: For a change, I know the answer. We did an open epicutaneous test many years ago for validation, unpublished and probably never will be published. But we were able to open application in the open epicutaneous test to sensitize in a dose-related manner with both petrolatum as the vehicle and water as a vehicle.

DR. MEADE: With chromate?

DR. MAIBACH: Yes, with chromate, potassium dichromate. Now, of course, that's the guinea pig and not man.

DR. MEADE: How many repeat applications did you do?

DR. MAIBACH: It's actually run as a 21 day assay. And then you have a rest period and then a challenge. It's really a remarkably good test. It's just a shame it's so much work.

The second part is an intellectual, religious, rhetorical issue. I'll go through the logic, but there is no solution. And it confounds a great deal of diagnostic -- of predictive testing both in the guinea pig and in man and in the mouse.

We don't have a method today to deal with the question that you bring up. And I'm sure you've run across it in your laboratory. If you use DMSO as a background subtract control. Which you certainly would do, you then have the irritancy of the DMSO; but you don't have the irritancy of the allergen that you study. In this case, it's chromate. The chromate has a separate irritancy.

So in essence, in order to do that in a guinea pig is very difficult. And you have the same problem in the lymph node assay because, if you want to do the irritancy control for the combination to both irritants; well, that's the test. So it's intellectual, logistical problem and probably produces many false positives in animal and the lymph node testing.

DR. HEERINGA: Dr. McMahon.

DR. MCMAHON: I'd just like to provide a few clarifications of my own to the last presentation.

It is true that in the background document regarding uncertainty factors that there was an application of a large uncertainty factor. But I believe I also stated that other possibilities were other uncertainty factors were possible there. And actually that is, as you have heard earlier, that's one of questions to the Panel regarding the magnitude of uncertainty factors and how they should be applied. That was but one example.

In citation of the 2001 Boukhman and

Maibach paper regarding the weight of the evidence, I note that the studies cited were from the 1960s. And you've also seen some newer dated data that we have provided in our presentation regarding minimum elicitation thresholds.

With regard to the IRIS statement that the concentrations of hexavalent chromium are likely to be lower than those required to cause induction, that statement is there. But they keep leaving out the last sentence which says, "However, these concentrations may not be lower than concentrations required to elicit an allergic in individuals who have been induced."

I just wanted to provide those clarifications to you. Thank you.

DR. HEERINGA: Thank you, Dr. McMahon. Dr. Chu.

DR. CHU: My question refers to the testing of Cr(VI) in water. As any investigator would know, applying an aqueous solution on the ear of a mouse is extremely difficult because it has fur. And a pure aqueous solution applied on it, it just doesn't stick. It may well be the reason why in other Ryan studies the SI surfactant and DMSO have been added in order to wet the skin. Could you elaborate, please?

DR. YOUNGREN: That is correct. But I just wanted to illustrate the fact that Dr. Ryan did go ahead and do water because he felt that there was an issue regarding the fact that, when we're talking about exposure really in aqueous solution, what we do comparable or have we put on a potentially a safety factor here because of that.

The other question comes, as I understand it, that you can't keep water necessarily on the mouse's ear. But also does that water with the compound also stay on the human. I don't want to get into that kind of discussion. But, again, that was where some of it come up. And, again, we're just reporting the data that is there.

DR. HEERINGA: Dr. Meade.

DR. MEADE: Just a very quick comment to that. I think that possibly the purpose of that was a little bit misstated there. The sole purpose of that paper was to find a vehicle that was appropriate for testing chemicals that are only soluble in aqueous solutions. So it was up front that was the issue for the paper being done.

DR. YOUNGREN: I agree with you totally. I'm sorry if I misstated that. I apologize.

DR. MEADE: One other thing I'd like to point out. Howard has reminded us on numerous occasions throughout the day of challenges to move the science forward. And the quote that has been brought up by Iain was in 2001. And the science has moved forward since then.

DR. HEERINGA: Just one minor additional point, Dr. Younger. Your projections of the prevalence or lack of prevalence of Cr(VI) sensitivity, I think selection bias is inherent in this sort of multistep process are enormous enough that I wouldn't trust that number. The exercise I understand. But I think the selectivity in a dermatologist's population and selectivity of application of the TRUE Test to dermatology populations. I think the 99.9 -- I don't know what the number is, but I think that particular estimate --

DR. YOUNGREN: Mind you, that's not of the whole population. That's looking at those who visit dermatology offices.

DR. HEERINGA: And we assume that we have randomly distributed applications of the T.R.U.E Test, too.

DR. YOUNGREN: No, we don't. We

already know that those are people that have been in some ways already chosen because there's an issue. You don't go to necessarily get tested. However, there will be some people, obviously, who will show up with a chromium positive, as Dr. Maibach has mentioned, where we can't explain why they did. In other words, that's not necessarily what they were going for.

But we have some other prevalence data for the general population which is the .08 percent that I talked about that will be presented by another presenter later.

DR. MENNE: It's a highly problematic exercise you're making there because we all know that very few individuals are patch tested in the United States. In Denmark, the 5 million inhabitants and the rest European area. We have a frequency in Denmark with the 5 million, it's 30,000 patch-tested a year. And it's the same frequency of chromate sensitivity as in the U.S.

Here in the U.S., you're patch testing 60,000 after 300 million. You can see, you know, it's pure nonsense, this calculation because it only depends on the patch test frequency. So you cannot do this calculation. And you should say, okay, you take out this picture. Because you go from the patch test -- you say that everybody who's chromate allergic will come to a dermatologist. And that's not true.

DR. YOUNGREN: But wouldn't you say that those are showing ACD or a large portion of those who were showing ACD would be going to see a dermatologist?

DR. MENNE: I don't think so, no. And particularly that's a great difference from one country the other.

DR. YOUNGREN: I'm going to ask a question. Why are there so many people that are patch-tested?

DR. MERENDA: Because they have allergic contact dermatitis. You know, you could say --

DR. YOUNGREN: But then that would say to us you have less of that.

DR. MERENDA: Let me give you an idea. For example, if you go to San Francisco and patch test the background population, 10 percent of the females would be nickel allergic. And, you know, that's not reflected in frequency of patch testing. Not at all. And all these people, they have intermitting contact dermatitis from jewelry. This is a nonsense exercise you're doing.

DR. FOULDS: I would agree with Torkil that it not only depends on seeing a dermatologist, it depends which dermatologist you see. There are many people who go to see a dermatologist with allergic contact dermatitis who are never patch tested in the

United Kingdom and are told that they have a constitutional or occupational induced skin disease and they'll have to give up their work. And if it goes on, well, that's because he has been born with the tendency and here's a little bit of steroid cream to treat them. It doesn't automatically mean to say that they are followed up by a patch test and investigation and avoidance measures.

DR. HEERINGA: Are there any other comments at this point in time? Yes, Mr. Morgan.

MR. MORGAN: I'm a little confused in the response, and I'm making an assumption. If I have the wrong assumption, I'll accept that.

But, Dr. Menne, you said that if you just tested 10,000 people in the San Francisco Bay area, I think it's the normal population, you have 10 percent positive to nickel. That's an assumption.

DR. MENNE: That's been done.

MR. MORGAN: Okay.

DR. MENNE: That's not an assumption.

MR. MORGAN: All right. But when I look at the prevalence data that I see coming out of the North American Contact Dermatitis for the last two years, shows nickel that population sensitivity is about 16 percent nation wide, which would lead me to believe that there's a higher propensity of people who have a problem would start into the system that ends them up being patch-tested. And so if you have a problem and you get there, because normally when I go to the doctor, I don't normally get patch-tested as a part of a routine physical.

DR. MENNE: Can we use time on this?

DR. HEERINGA: I think that I'd like to draw -- I sort of kicked this off. I think it's an issue that we can pick up again, but I want to make sure we move along to some of the other public comments. It was just an issue that the prevalence rate is obviously at some point in time an important factor. But I think we all agree there's enough disagreement around the table as to what that ais and how to estimate it.

Are there any other questions for Dr. Youngren, Mr. Morgan, or Dr. Maibach?

At this point in time, I'd like to take a short break. Paul, do you have anything?

Let's take a 15-minute break and return here at just prior to 20 minutes to 4.

And if I could, could I ask from the audience Paul Cooper and Deborah Proctor, Joel Barnhart, and Warren Sickle, Jane Vergnes, and Richard Wiles, could you touch base with us if you have travel difficulties, if you're planning to be out of here this evening? These are additional public commenters who are ordered in sequence here. And I want to make sure that we can accommodate you if need be.

[Break at 4:05 p.m.; session reconvened at 4:25 p.m.]

DR. HEERINGA: Before we begin with the public comment this afternoon, Dr. Gary Burleson has arrived. As I indicated this morning, he was going to be delayed in getting here. He's arrived now. Let's give him a chance to introduce himself.

DR. BURLESON: My name is Gary Burleson. I'm from BRT, Burleson Research Technology, a contract research lab in Raleigh, North Carolina.

DR. HEERINGA: Thank you very much.

At this point, I'd like to continue with the public comment. And the next public commenter who is scheduled is Paul Cooper of the University of Toronto, and he's representing Osmose, Incorporated. Dr. Cooper.

There was a handout of a manuscript or a draft report from Dr. Cooper that was distributed to members of the Panel and should be placed in the docket as well.

MR. HORTON: I'm John Horton, director of commercial development for Osmose, Inc. We are a manufacture and marketer of wood preservatives worldwide. And at present and for approximately the last 10 years since 1993, I believe, Osmose has been the only EPA registration holder for ACC -- acid, copper, chromate -- wood preservative in the U.S.

Over this time, Osmose distributed only a small volume of the ACC wood preservative material for treatment of mainly wooden slats that were used in the construction of industrial cooling tower equipment.

We have asked that Dr. Paul Cooper, Professor at the University of Toronto, Faculty of Forestry and Wood Science, come here today to present an overview of chromium reduction process of ACC-treated wood as compared to the CCA-treated wood.

Professor Cooper will base his comments directly on both studies that he conducted that were sponsored by Osmose and his own independent research conducted at the University of Toronto.

And if anyone has a question after his presentation that I might answer about industry, I would be happy to address it.

DR. HEERINGA: Thank you very much.

DR. COOPER: I thank you very much, Mr. Chairman and Panel members for allowing me to come here today to talk about some of the work that we've been doing.

We've been working on the reactions of the chromium preservatives but primarily, chromated copper arsenate and wood for some time. And as John mentioned, we've done some amount of work on the acid copper chromate.

So it's mainly to give a bit of insight into what's going on with the interactions with wood and to get some comparison between the two preservative systems.

So just, again, I'm going to give a little bit of background that has been given but maybe in a little different way. What we have here is very dilute solution of a preservative system in water that has got a high amount of hexavalent chromium which is yellow in color, and that is then reacted in pressure vessel or impregnated into wood in a pressure vessel. And that's then followed by a chemical reaction which we loosely term as fixation reactions.

So that shows some of the structure of wood. So just to give you an idea, this void space within the wood is totally filled with the treating solution. And then the chemicals start to react with the chemicals within the cell wall and with each other, and are deposited or precipitated either on the surface of those cell lumens or within the cell wall itself.

The reactions have been mentioned a little bit before. But primarily as was mentioned by Mr. Morgan, the chromium is a fixing agent. It really drives this total insoluablization process of the other chemicals. And during this process, oxidizes wood components. And, in fact, it is reduced to trivalent chromium.

In chromate copper arsenic, the arsenic plays quite a important role in the rate of this reaction because it allows precipitation of chromium arsenates which help to drive the reaction and speed up the reduction of chromium. In the absence of that, in acid copper chromium, for example, it's a reaction between the chromium and the wood components. And in going through that reaction, the pH increases the acidity is decreasing within the system. And that allows copper to ion exchange and otherwise react with the wood and become less soluble within the wood.

Now, the way that we follow the reaction -- this picture is not very clear. But we actually squeeze chemical out of the wood structure at different times after treatment and analyze it for hexavalent chromium for copper, for arsenic, and CCA. And we analyze that to get an idea of how the reaction is proceeding and how quickly it is going. And so that way we can look at the different variables that affect this fixation process.

You've seen this slide twice before already. But I think the point I would like to make is that these variables which have a tremendous effect on how fast the chromium is reduced, and especially temperature, these have been well-explored for CCA. There have been many, many studies over the years. And we have a pretty good handle on what the variables are. And that sort of work, I think, will have to be done for acid copper chromate in order to determine what though factors and effect are.

I'm sorry for this. This, though, does show the rate of change of concentration with time. So the very faint blue line is chromium, hexavalent chromium, being reduced over time within the cell. The green is the arsenic, and the red is copper and chromate copper arsenate. So that's the type of information we develop from the ways we follow fixation.

And the temperature factor was mentioned before very strong and has a tremendous influence with CCA. And I think we can expect that same sort of thing with acid copper chromate that we're going to have a very strong. And I'll show a little bit of that type of result as well.

This shows graphically the comparison between copper chrom arsenate in yellow and acid copper chromate in the green. And I'll show the data next just to confirm what was mentioned by a couple of the previous speakers that acid copper chromate takes longer for the chromium reduction because it has higher chromium content and because it does not have the arsenic to help to take the reaction to its equilibrium.

So if we look at some of the times that we have found in laboratory testing and field testing where we compare the time to complete, and that's more than 09.5 percent of the chromium being reduced in the wood, the times are a bit longer than were mentioned earlier. But the acid copper chromium, for example, with a 1 percent solution at about 70 degrees Fahrenheit with the .4 pounds per cubic foot -- that's the first two rows --

about 34 days to get to that 99.5 percent chromium reduction versus about 18 days in CCA-treated pine.

As we increase the temperature to 50 degrees centigrade, or about 120 degrees Fahrenheit, the time is shortened drastically to 32 hours in the case CCA and 48 hours in the case of acid copper chromate. And if we increase the retention of the preservative in the wood, go from 6.4 kilograms per cubic meter to 20, we extend the reaction times quite a bit with both systems but especially with the acid copper chromate.

We've done very limited comparisons of species. And these show the rates of chromium fixation, now expressed as percent of total, and we can see that the species effect and the sap wood of pine and the sap wood of Douglas fir which are the two bottom limes are, quite similar and they take quite a bit longer to go through these reactions than the hardwood which is the center part, the dead part, of a Douglas fir tree which reacts much more quickly because of the chemicals and extractants that are present in the heart wood of the species. So there are species differences as well.

We've done some very limited Kim wipe dislodgeability tests or wipe texts for hexavalent chromium. This was done at the treating plant. So we were kind of limited on the ages of the wood or the extent of the fixation that had occurred. But the time on the bottom axis is the time after removal from the treating plant, and on the vertical axis is in ug/cm2 of hexavalent chromium.

And what we have found is that the ACC, because of its higher chromium content, does have a higher amount of hexavalent chromium that is dislodged up until, as was mentioned before, the reaction is almost complete. So it's going to be a little bit more of an issue with acid copper chromate than it was with chromated copper arsenate in terms of the amount of material that could be wiped from the surface.

This shows really the same data but now expressed as percent fixation. And it sort of spreads things out a little bit because, in this case, again because the chromium content is higher in the acid copper chromate at the same percentage of reduction, we have more free hexavalent chromium in the wood in the latter preservative. So, again, we get this difference between them.

The tables in the paper that I prepared give numbers that you can look at. And just to put it into context to some of the numbers we have seen today, at about 95 percent of the chromium reduction in CCA and about 98 percent of the chromium reduction in acid copper chromate, we're down in the order of .02 to .03 ug/cm2 which is approximately the same as .0189 that was looked at.

There's one thing that we have to be aware of, and there certain circumstances where the chromium that's reduced to trivalent chromium can be reoxidized to hexavalent chromium. And the example that I have here is with bleaches, deck brighteners and oxidizing agents that are used to cleanup decks. And anything that contains something like sodium hyperchloride sodium percarbonate, or sodium hydroxide, will cause some of the chromium in treated wood to be reoxidized to the hexavalent form. That's something we have to be aware of both for CCA and for acid copper chromate.

The next slide just gives some of the quantification. If we compare the amount of chromium that we will wash off a square meter of deck if we just apply water to it and then compare it with these deck washes, the ones in reds show that sodium hydroxide will remove about 15 times as much chromium. And with the other more aggressive oxidizing agents, it will remove even higher amounts. And most of this chromium, in fact, is hexavalent. So this is something that has to be considered in the application of these post-use treatments.

Now in Canada, we have an issue with temperature in treating. We have very limited time for treating where the testimony temperatures are high enough to advance these reactions fairly quickly. And as mentioned before, it can take weeks and even months for the reactions to take place at low temperatures. So virtually every treating plant in Canada has gone to an accelerated fixation process where they actually steam or kiln heat at high humidity the wood in order to make sure in the case of CCA that the reactions are near complete before they're removed.

This is not a common practice in the U.S.A, but it may be something that may be more necessary if we go to a system that takes quite substantially longer for the reactions to take place.

There was a mention made of the diagnostic test for fixation of chromium which is the chromium tropic acid test which is the spot test on the upper left which allows us to tell when the hexavalent chromium content in the wood drops to about 15 parts per million. Then we can't see the purple color reaction any more. We developed and worked with a more sensitive method that uses diphenolcarbozide which allows us to take a small boring of wood and leach it very briefly in water and react it with diphenolcarbozide to get a quantitative estimate of how much unreacted chromium there is.

The point I'm making here is, again, this quality control is something that's becoming mandatory in the Canadian treating plants. And it's something that may become more necessary here as well.

Just to be sure that before the wood is moved off the protected storage within the treating plant and trucked to a retail yard and perhaps gets to the ultimate consumer, there's going to have be to some way of checking to make sure that these reactions are complete if you want to make sure you're down to these levels of surface availability that you've been talking about today.

Just to sum up, I'd like to say that the acid copper chromate does take longer for these reactions to complete, about 50 percent longer or more depending on the conditions. Until it's completely reduced, the amount that's available on the surface is higher in acid copper chromate than in CCA. Under concern conditions, the Cr(III), whether it's in any type of chromium preservative, can be reoxidized. And this has to be taken into account.

And it's my feeling that accelerated fixation, controlled fixation in combination with some quality control procedure to monitor the reduction of chromium may be needed if we're going to work with a system that does take somewhat longer to react with the system we're familiar with, the chromated copper arsenate.

Thank you very much for your time.

DR. HEERINGA: Thank you very much, Dr. Cooper.

Are there any questions from the Panel for Dr. Cooper on his presentation, ACC or the Osmose?

DR. FOULDS: I was interested in the effects of these different deck washes and brighteners on your sort of CCA-treated wood. Is there any information available on the ACC-treated wood in a similar way?

DR. COOPER: Well, no. Because the acid copper chromate has not been used, I would say, in North America for this type of application, there is no practical way to test it. Now, to test it in the laboratory like we did, it could be done but it has not been done. But my expectation is that the chromium would be just as susceptible or similarly susceptible to it.

DR. FOULDS: Because in some ways, there are quite sort of alarming levels of hexavalent chromium being released by the sodium hydroxide. And presumably you anticipate equivalent levels with ACC. Obviously, the data isn't there. Are there warnings on these sort of deck washers and brighteners about any potential risk of this at all?

MR. COOPER: I don't. Perhaps John could answer that. I think that the industry is certainly aware of this issue. And I believe that they've withdrawn this type of product for treated wood products. But I'm not sure how well the consumers are informed of this.

MR. HORTON: When the work first came out, we did recommend that these types of oxidizing, brightener cleaner products not be used on the wood. We just recommend for cleaning the treated wood products out there with chromium in them just a mild soap and water now.

DR. HEERINGA: Dr. Menne.

DR. MENNE: I just wonder, how did you get the chromate into the wood? Is there any pressure tanks? How is the process?

DR. COOPER: I should have spent a little more time maybe on I think my second graph or second figure. I guess we're going to back up to it.

Down in the bottom right-hand corner, that's a pressure vessel or a pressure retard. So the wood is stacked and put into that vessel. A vacuum is applied to draw all of the air out of the wood and out of the pressure vessel. That vacuum is used to draw the solution in. It's pressurized at 150 p.s.i. And I should know what that is in kilo pascales, but I'm not too sure. It's fairly high pressure.

After the treatment, which could be anywhere from less than an hour to several hours, the chemical is drained. And a final vacuum is applied to sort of remove the excess solution that is on the surface of the wood.

DR. HEERINGA: Not seeing any additional questions, I want to thank you very, very much for the presentation.

At this point in time, I'd like to move on to our next public commenter. And that is Dr. Deborah Proctor of Exponent, Inc., and she's representing Tierra Solutions, Inc. Dr. Proctor.

Do you need a little help setting that up, or are you ready?

Just a note, please feel free to bring them to Paul and myself and we'll get them loaded for you.

DR. PLEUS: I have a question. I don't know if we have time. I had a question for Dr. Cooper, and I don't know if it's worth doing this for the moment.

DR. HEERINGA: Yes. Dr. Cooper if you don't mind coming back up to the microphone.

DR. PLEUS: On your page 10 of your report, it says Table 6. I think that was one of the slides that you had presented on the effect of different deck washes, brighteners on relative leaching on CCA?

DR. COOPER: Right.

DR. PLEUS: And then you have the ratio of leached element compared to water. The question I have is: Is that Cr(VI) that was measured as species?

DR. COOPER: We analyzed the total chromium and Cr(VI). And I should have put here the ratio. But it was like more than 80 hexavalent chromium,.

DR. PLEUS: More than 80 percent.

DR. COOPER: Yes.

DR. PLEUS: One question I have is just maybe the underlying raw data for something like that. Would one way to do this maybe go back to Table 4 or Table 5 and then just kind of apply some of those ratios to some of these numbers? Is that a fair way to do that to get a quantity?

DR. COOPER: I don't think there's much relationship. The Tables 4 and 5 were the fixation at different times. And I believe that the brighteners, the bleach effect, is totally different. They were all on material that had been completely reacted and fixed and in some cases been in service for some time. So I don't think there's any relationship between them.

DR. PLEUS: I'm just trying to come up with a value, and maybe they're not swipe samples or something like that.

DR. COOPER: I see what you mean. Yes. Unfortunately, we didn't do the wipe test. And what we did was just simply brush, physically brush with a certain volume of water and compared that with the same amount of the deck wash followed by a wash with water. That was the basis that we did that.

DR. PLEUS: Thank you.

DR. HEERINGA: Dr. Cooper, one more question. Dr. Isom has a question for you.

DR. ISOM: Perhaps for you, and then maybe the EPA with regards to the product, pressure-treated products that are on the market and perhaps to reach the market. Does the industry have a standard with regards to how long they fix the products? Does that vary from manufacture to manufacture? If I go down to the lumber yard and buy pressure-treated wood, does it vary depending on the source and what I get?

DR. COOPER: Well, I think it would vary to some extent. There is certainly a minimum. I couldn't say it's mandated by anyone, but it's an industry standard. But I believe it's 48 hours that they keep it protected on a drip pad so that anything that drips off can be recovered.

But the way that it was alluded to in a sense that the way that the construction goes is quite different from the treating patterns so they will treat all year round. So some material may be in inventory within the treating plants for months before it gets called by the Lowes or Home Depot to come to their place. So I'd say there's a wide range from, it could be as low, hopefully not, but as low as 48 hours to several months before it gets out to the retailer.

DR. ISOM: So the consumer would potentially be exposed to different amounts of Cr(VI) depending upon the source and when they buy it.

DR. COOPER: The hope is that by the time they receive it, because these reactions are just going on, chugging along all the time. And the hope is that it will be completely reduced before the consumer gets it. I don't know of any real tests. We've looked at stuff that we've bought. We've looked at stuff that's been in service for short time and have not found hexavalent chromium. But that's not to say that it's impossible for it to occur.

DR. ISOM: So with regards to licensing, is there a standard that you look for there? Or is it just the product dipped in this or pressure treated and that's it? Or do you have a standard with regards to, let's say, the temperature it should be treated and how long?

DR. COOPER: Yes. There are process standards, for example, with American Wood Preservers Association, that describes the pressures, vacuums, times, temperatures, things like that, and the amount of chemical that should be in the wood.

Then there are, I would say, more like industry standards in regard to how the plant is operated to be safe. And that's the one that involves the storage times and so on. The American Wood Preservers Association has the chromotropic acid test as one of their standards as a recommended standard. But I don't believe it's mandated by anyone.

DR. HEERINGA: Thank you very much. One more question for Dr. Cooper.

DR. BAILEY: What sort of protective equipment are worn by your workers in pressure treating your lumber?

MR. HORNER: Well, in today's treating plant environment, they do wear PPE. And it would depend on their responsibilities at the treating plant. There are people who actively do get close to the freshly treated wood. But typically today, the wood is brought out either on automated conveyor belts and moved on a transfer table. And in that case, the wood bundles. And they are all still in the bundled form. They are picked up with a forklift and taken to a holding area and set down.

So relatively speaking, in today's plant environment, because of the need also to turn high productions around, there really is hardly any at all actual real contact with the wood itself by the workers.

Now after the material has sat for a while and it is moved out, lets say, from the holding area, the 48 or 72 hours, and then moved out to a storage yard, it will still be covered in a paved area, there might be some handling at that time. But, of coarse, but the workers are given gloves to wear and in some cases aprons. Typically, at that time the wood is not wet or dripping.

Things have changed quite a bit over the past 20 years in the industry. And in some cases, the wood never even leaves coverage until it is shipped out to retailers. Some of our plants are totally enclosed in an environment when it's moved around and kept in holding in a controlled temperature environment for however long before it's released.

So exposure should be minimal. And, again, there is always training and proper PPE equipment for whatever exposures would be encounter at the plant.

DR. BAILEY: Thank you.

DR. HEERINGA: Thank you very much. That's very helpful.

Okay. Let's turn to Dr. Proctor.

MS. PROCTOR: Ms. Proctor, actually.

I am an environmental risk assessor and a toxicologist. And my experience in this arena comes from managing and evaluating the chromium contaminated sites in Hudson County, New Jersey. I represent or work with one of the responsible parties which is TR Solutions, Inc. It's the successor to the environmental liabilities of Diamond Shamrock.

Could you go back, please.

I have also been involved in both the design and implementation of both the Nethercott 1994 study and the Fowler study. And the Fowler study is the basis for the current New Jersey allergic contact dermatitis standards.

My objective here today is to provide perspective on the use of human exposure data for environmental health risk assessment. At this point, we have about 15 years of experience in evaluating the potential allergic contact dermatitis hazard from hexachrome in soil and in surface puddles in New Jersey.

I have some updated data on the incidence of hexachrom allergy in the U.S. clinical population from the North American Contact Dermatitis Group. And I want to talk about environment health assessment considerations, exposure conditions, and uncertainty factors. And to the extent possible, based on the limited information that's available, address wood contact specific exposures today.

I'm going to talk about the 10 percent MET. And I'll try not to reiterate too much of what has already been said. But my spin on this is a little bit different. I am talking a little bit specifically about how these data are applied to environment health risk assessment. I know wood is very different from soil. But I think there's a lot of similarities here.

I'm going to talk a little bit about the human sensitization data. Perhaps you all know it better than I. But we have looked at this data for application in New Jersey. And then just from a risk assessment perspective, uncertainty factors and kind of doing a reality check on what has been proposed by EPA.

I think the concept of a 10 percent MET, or minimum elicitation threshold, may have originated back in 1989 with the NJDEPs derivation of dermatitis-based standard. At that time, they took historical patch test data coming from the 50s, 60s, 70s, and somewhat into the 80s, and estimated the 10 percent response threshold. So it's an elicitation-based standard that we apply in New Jersey. And I tell you that today we're cleaning up chromium contaminated soils for hexavalent chromium.

It was assumed that a 10 ppm patch equalled 10 ppm in soil and that the elicitation threshold was 10 ppm. And it was generally assumed based on the 1966 study of Kligman that it would also be protective of induction. To specifically address this issue, the Nethercott, et al., study was done to generate state of the art data that could be used to describe the dose response relationship.

As I think Howard said, some things seem simple until you realize them. It took us several years to realize that the correct dose metric was mass per area not concentration when evaluating the elicitation threshold.

What we have considered in New Jersey, it is what is used for the Massachusetts allergic contact dermatitis standard, and I think it's probably the correct dose metric as well for hexavalent chromium in treated wood.

On the one study by Freedman by 1983 DNCB that mass per area was more important than the total area exposed or even the total mass, that concentration in the mass per area was the critical dose metric.

Just briefly on the Nethercott study. I know we've gone over this over and over. But I want to mention that, when we started this study, we were really seeking to identify hundreds of individuals in the United States that could patch test as part of this study. We were relatively disappointed when we could only find 102 volunteers. We were even more disappointed when half of those almost weren't allergic in the first round of testing to the TRUE Test patch which we considered the standard diagnostic patch at 4.4 micrograms of hexavalent chromium per centimeter squared.

I guess there's been some debate as to what exactly the diagnostic patch test concentration. As when we conducted this study, we were under the opinion that it was 4.4. And we did an independent validation of all of our patches at a separate laboratory to confirm the patch test concentration. So I can tell you that our concentrations are in fact 4.4 as what was our upper bound for hexavalent chromium.

We also tested trivalent chromium as well. However, only one individual had a reaction which the dermatologist scored as doubtful. They re-patch tested that individual subsequently. And he had a negative reaction.

So what Nethercott allowed us to do at that point was to determine a threshold in the mass of allergen per cm2 for each subject.

Sorry. This is pretty hard to see. The bar of calculating a 10 percent MET had been set by the New Jersey Department of Environmental Protection. And so that is the standard by which we used. We can see that about 5 out of 54 individuals reacted by the second dose level which was 0.088. I apologize for the quality of that table. And which is consistent with our mathematical extrapolation. The 10 percent MET was 0.089 micrograms of hexavalent per chromium squared.

For improved picture quality, I just wanted to give, for those of you who are not dermatologists and don't see what we're looking at. There's a little square in the middle of that circle. That is a weak reaction. I picked out a couple of the pictures. The reaction at the lowest dose level which is the reaction that has been selected by EPA as the basis for their -- I can't remember their acronym. But basically their starting point for dividing by uncertainty factors was also a weak reaction.

Number 8 in this picture is a strong reaction. You can see it's a more obvious red dot. That's all I just wanted to show you for a little bit of perspective.

In the Nethercott study, we confirmed that hexavalent chromium sensitized individuals respond to serial dilutions of hexavalent chromium in pretty much a linear manner. Because about half of our volunteers did not respond to the diagnostic patch test, 4.4 ug/cm2, we believe that the Nethercott study probably represents a conservative measure of a 10 percent MET for elicitation among presensitized individuals.

If we compare the 10 percent MET in Nethercott to that from historical study which was done by Scott and Proctor in '97, we find that the Nethercott MET is about 10 times lower. These are studies that are quite a bit older, though. They are mostly done with Finn-Chamber-type dosing devices.

We also did three rounds of testing which was specifically performed to reduce the occurrence of false positives. And then as I believe has been said on multiple occasions today, the TRUE Test patch is an effective delivery device.

These are just some additional details about the study.

About 20 percent of the people who were a part of the study were in construction-related industries. 15 percent had past or present atopic dermatitis during the course of the study. And the most sensitive subject who is the basis of the standard was a very hypersensitive individual. He reacted to a lot of different allergens.

And in talking to him, he actually started in the Fowler study and couldn't actually finish because dermatitis from other exposures in Round 2 precluded his involvement. He told us he even got dermatitis from hot showers. So he's a very hypersensitive person among atopic individuals.

In about 1995, NJDEP decided to change their approach from a soil to skin adherence to something that was protective of puddles. This was done for a couple of reasons. Perhaps this is only two of them. One is that there were observations in many, many locations of yellow puddles. Hexavalent chromium is yellow in solution.

Also consistent with what was said from OSWER today, there were questions of bioavailability and how much hexavalent chromium could be solubilized in soil. Specifically in order to address this issue, the puddle exposure scenario, the Fowler study was conducted. And it is the basis of the current New Jersey standards. We clean up soils today based on this study. And I'll tell you how.

In the Fowler study, the aim was to estimate the potential for allergic contact dermatitis from dermal contact from water containing hexavalent chromium in an environmental exposure scenario. Not specifically to identify whether or not, if these people sat in these exposures for long enough, they would get a reaction. But we had generated a scenario which we thought was very conservative for what environmental exposures could potentially be.

Twenty-six people participated in the study. They all also participated in the Nethercott study, including as I said before, the most sensitive individual from the Nethercott study. Concentrations hexavalent chromium in water were 25 to 29 milligrams per liter and the pH 9.4. Both the pH and the concentrations were designed to kind of simulate the upward of bound worse case puddles that had been measured in New Jersey.

We did two rounds of testing. This is an example of the test scenario. We had these boxes. And the individuals who participated put their forearms in boxes. On the one side they had hexavalent chromium. On the other side, they had the buffer solution that was used to make the hexavalent chromium solution. As you can tell, the water was yellow. So anybody who knew that chromium was yellow, wasn't blinded as to the exposure.

People reacted in both rounds. In the first round, 16 of the 26 individuals developed no response due to 30 minutes of submersion exposures on three consecutive days. Those who responded in Round 1, with the exceptions of those who weren't available, participated in Round 2. And it only ended up being five individuals could participate in Round 2.

In Round 2, we switched arms. So if you exposed your right arm to chromium in

Round 1, you exposed your left arm to chromium in Round 2. The reactions that were observed. There was question as to whether or not they were an irritant or an allergic reaction. Biopsy samples were collected and analyzed by a dermatological histopathologist. And they were considered to be indicative of a transient or weak either allergic or irritant reaction. It was an acute eccrine reaction. So basically in the sweat gland the reaction was observed.

Here's a picture, although granted not to good in this quality. This is about the worst of the reactions. And you can see there are little red dots all over the forearm of this participant.

Basically what was concluded is that the endpoint that we were trying to protect was an eczematous reaction of like allergic contact dermatitis. The observations that we had in the Fowler study, was not of eczematous dermatitis but rather of some transient effect. And because the exposure scenario was considered to be relatively extreme for environmental exposures to standing water, it was treated as a NOAEL for allergic contact dermatitis.

However, I want to caution. If you read the Fowler study in detail, we do identify that it is possible that it was an allergic reaction that was observed. And maybe in some individuals, it was allergic in some. It was an irritant. It is difficult to know.

In New Jersey on a site-by-site basis, we determine what the leachability of hexavalent chromium in soils is. Just to give you a little more background, there's about 210 cites in New Jersey where chromium has been used as fill material or processing residue. It has varying insolubility from site to site. So we do a water shake test, which is an ASTM test, at multiple dilutions. And then we calculate the target concentration at a liquid to solid ratio of 2 to 1, simulating very little amount of liquid associated with the solid. And then, you know, as the liquid-to-solid ratio goes down, the concentration of hexavalent chromium as well goes down.

So the idea is to determine the hexavalent chromium concentration that is consistent with 25 ppm of hexavalent chromium in solution. And that typically gives us cleanup levels in the range of 200 to 700 ppm of hexavalent chromium.

There is variability around that. We have had levels as high as 20,000 because the hexavalent chromium has been extremely insoluble. And in levels lower than that, I think the lowest is 99 at one of our cleanup levels.

So that's how we determine what

needs to be cleaned up in New Jersey to some degree that in addition to inhalation-based standards and soil ingestion based standards. In reality, the highest hexavalent chromium we've ever measured in any of the puddles is 16 parts per million. And that was at a site where the -- you know, we have concentrations well over a thousand parts per million of hexavalent chromium in soil. So this is a relatively conservative approach. Perhaps the conservatism comes from the liquid-to-solid ratio in the shake extraction test.

Massachusetts in 1998 also set a similar standard. It's an elicitation-based standard. They used the Nethercott study. They assumed 100 percent bioavailability of hexavalent chromium. And they calculated a soil standard of 170 mg/kg. The difference between what Massachusetts calculated and what was calculated in Nethercott, et al., for application in New Jersey, those are both soil-to-skin-adherence-type standards. Massachusetts used a higher soil adherence rate, loading rate, for soil on skin.

One thing that was asked of the Panel was with regard to soil matrix effects and what are the considerations for bioavailability. In 1993 we did a study, Horowitz and Finley, where we used real human sweat to extract hexavalent chromium from our soils in New Jersey. We did a 12-hour test. The sweat-to-soil ratios were 5 to 1 and 20 to 1. And we tested concentrations of hexavalent chromium between 6 and 1,240 parts per million. Bioavailability was less than .1 percent.

If you do the same test with water or simulated sweat that doesn't contain an organic component, you can get much higher extraction levels like 30 to 70 percent. So what we believed was happening is that the hexavalent chromium is reduced by the organic components of the real sweat to the trivalent state.

I want to transition here just a little bit and talk about the human sensitization or induction data. Kligman in 1966 did the human maximization test. The actual calculation of the 5 percent response level was not done by me. It was done by another author. Schneider and Akkan 2004. And I've converted this. This is different than what Dr. Youngren presented because I converted it to hexavalent chromium and she presented in terms of potassium dichromate.

So the dose in the human maximization test was 39 ug/cm2. It's based on this data that we assumed that our elicitation-based standard would also be protective of sensitization.

The diagnostic patch test -- I mean, perhaps, I'm wrong. Back when we did the Nethercott study, we believed it was 4.4

ug/cm2. Other information has been presented here today to suggest 23 ug/cm2.

And I asked Dr. Fowler just recently if he thought that the patch testing could induce sensitization. And his statement was that the risk of induction is believed to be minimal at this exposure. And I just want to remind that this is an occlude exposure which is coursed for 48 hours.

So while I don't want to spark another tremendous debate, I wanted to mention the incidence of hexavalent chromium allergy in the U.S. population. It's an important risk management decision. And although hexavalent chromium is a strong sensitizer, I question whether the fraction of the general population that is allergic to chromium is very large.

There is no U.S. general population data. Let me make that clear. We could attempt to gain some knowledge about what that number might be based on the clinical incidence rate in the United States.

To get a little bit of additional data for your information, I asked the North American Contact Dermatitis Group physicians to search their data base for the most current data on positive reactions to hexavalent chromium. And this is unpublished data which I can't publish without their permission. So you might want to ask them before you utilize this information as well.

In that time period, that's to current, from 2001 January to current, about 6,000 people were tested. The percent with positive responses was 4.1 percent. However, the percent that were determined to be relevant was only 24 percent. That is people with definite, probable, or past exposure to hexavalent chromium. So there may be a fracture of those who also are relevant, but they don't really know exactly why it's a positive reaction.

And it's also important to note that this could be an underestimate of clinical sensitization because the test which is used, which is the Finn Chamber, using the .25 percent potassium dichromate, is lower. And it's possible that there are people who are allergic to chromium who just don't react to that low level.

In 1998, we attempted to get a handle on what fraction of the population, general U.S. population, was allergic to hexavalent chromium. And at that point, we estimated about .08 percent. The clinical prevalence rate of 2 percent was used at that point. That was based on '92 to '96 North American Contact Dermatitis data. 50 percent of the positive reactions at that point were determined to be not relevant by the physicians.

And then we applied a

clinical-to-general ratio which is definitely uncertain. But basically what we did is we looked at data from two Italian studies, one of a clinical population and one of a general population conducted in 1984. And the difference between the clinical population and the general population as far as allergic reactions to hexavalent chromium was about 12. And I don't know if that ratio is applicable in the United States. I don't know if that ratio is applicable over time. But that is the number we used to get a general handle. And based on that, we calculated a rate of .08 percent.

Now in Hudson County, New Jersey, which is where these 200 chromium sites are and where they have been since the turn of the century, basically uncovered, exposed, anybody could come in contact with them. And this millions of tons of impacted soil material. From the minimum of the 1940s to the 1980, this was uncovered.

So we looked for people who were allergic to hexavalent chromium in this general population, and we couldn't identify any by calling dermatologists throughout the area. Also from '92 to '93, the New Jersey Department of Health attempted to -- well, they did a biomonitoring study where they collected urine samples. They also tried to identify individuals who could be allergic to hexavalent chromium. They surveyed 2,224 people. Twenty-three were identified for evaluation by a dermatologist. And then I think two were patch-tested. But none of them were allergic to chromium. So if you say zero out of 2,220, that would be a rate of less than 0.04 percent.

And granted, not everyone in that population was tested for hexavalent chromium. But the objective was to find people who were allergic.

The real challenge is extrapolating these data to human health assessment. So I think that we have a particularly large challenge in this case. Risk assessors do anyways because typically we work with toxicology data that's designed to calculate what a low observed effect level is. Whereas with dermatitis, a lot of times we're working with data that's designed to make sure that we can identify people who are allergic in the human population or identify sensitizers.

Importance factors in applying these data to the evaluation of wood is the consideration of wood to total occlusion in patch testing. When people are exposed to wood, they could get residue on their skin. I clearly assume so. That was a picture of my daughter hanging from the fort that is made out of CCA-treated wood. So I know there is going to be dermal contact.

But is the type of penetrating

dermal contact that you would get from total occlusion from 48 hours? This is a factor to consider. I think that that's probably kind of conservative with regard to real world environmental exposure.

I wanted to talk about uncertainty factors. The intraspecies uncertainty factors. So that's sensitivity within the human population. For an induction-based standard, I think the ten-fold factor is warranted. That would be the typical default. For an elicitation-based standard, I think that a one-fold factor, I would suggest, is relevant because what we're working with already is a highly sensitive human population. So we're kind of looking when you're doing an elicitation standard, you're look at the sensitive human subpopulation. And that would be consistent with the approach that's been applied in both New Jersey and Massachusetts.

If you want to extrapolate from a 10 percent minimum effective dose to something that you would make akin to a NOAEL, I would suggest considering taking the lower confidence limit. That would be something similar to what EPA does with the benchmark dose modeling approach. For Nethercott, et al., the 95 percent lower confidence level is 0.052. I mean it's just a suggestion here to consider.

Interspecies species. So you only would use an interspecies uncertainty factor when you're going from mouse to human in this case. So it's only specific to the LLAN-based proposal. I think that the 10-fold default factor, which is typically used for intraspecies, is used when there is really no human data available and when humans are considered to be more sensitive that the species tested.

I don't believe that that's really

the case here. We have quite a bit of human data. And the human data that does exist suggests that the mouse EC3 value in the LLNA is generally consistent with the human maximization test for 5 percent response.

And I think that Felter, et al., 2003, shows relatively well that that is that is the case for many chemicals.

And for hexavalent chromium specifically. This is the Schneider and Akkan study, 2000, which I found very interesting. I'm not going to pretend to know a lot about the LLNA test. Conveniently, they had all their numbers translated into ug/cm2. They used six different studies, six different studies than EPA used to calculate the dose which caused an EC3 level effect.

In addition to the comparison here of human and mouse data, I'd like to question whether or not it's appropriate to look at only one study or whether it's appropriate to look at all of the studies that have done LLNA and take a composite of all of the literature if that's going to be the basis for the standard rather than focusing on just one study.

So if you compare the LLNA to the human maximization test, you can see that in terms of potassium dichromate, the doses are very similar which cause effects. If you convert those to hexavalent chromium, because potassium dichromate is only about 35 percent by weight hexavalent chromium, you get numbers of 41 and 39 ug/cm2. So I think that there's really good correlation between species for hexavalent chromium, and that you ought to consider an interspecies uncertainty factor of 1.

Matrix factor. And you know Susan put up the suggestion of a factor less than 1. And that was consistent with what I had considered as well. And the following reason, when you're considering the LLAN-based standard, using the Kimber '95 used DMSO as a vehicle. And let's face it. DMSO is extremely effective at moving chemicals through the skin.

I don't think that the matrix of hexavalent chromium that could occur on wood would likely be anywhere near as effective. Similarly, if you look at a patch-test-based matrix effect factor, the patch test is designed for hexavalent chromium to be absorbed through the skin. The T.R.U.E Test patch or petrolatum both, I think, are going to be effective more likely than not than a residue on wood. And then the 10 percent METs, I'd like to point out, are typically higher in acids than in alkaline matrices.

This is specifically the data I'm talking about. And granted these are older data. I do a lot of inhalation toxicology work where it's extremely evident that hexavalent chromium is not one chemical. And that the various forms and pHs of hexavalent chromium can exist is really very important factor in toxicology.

And if you look real briefly as these elicitation standards, these 10 percent METs, for alkaline conditions, a 10 percent MET is about .57 to .63 ug/cm2. But in the data where hexavalent chromium is in acid, two out of three of the METs are 10 or higher. And then in neutral pH, it's kind of in the middle, 1.63. And in petrolatum, it's the same. That was something that never jumped out to me in those data before, but I think it's something that might be important to consider.

We see a lot of cement dermatitis. Cement is extremely alkaline. It's possible that in alkaline conditions, hexavalent chromium is a more potent sensitizer or elicitor of ACD.

There's an uncertainty factor for exposure conditions. And a lot of these uncertainty factors, I want to point out, were initially proposed for skin care products. Things that you put -- deodorant you put on your under arm or lotion you put on every day. So it's something that is not necessarily directly applicable to wood which could probably, you know, get contacting with your hands or your legs or your feet. But it's not necessarily more sensitive or susceptible to skin.

I do believe the skin condition is a very relevant concern. When we did the Fowler study, one individual had a bad scratch on his arm which really wasn't apparent until we dumped his arm in hexavalent chromium. And then his scratches were lit up like you can't believe. So I think that having the skin intact is a very important consideration.

And then multiple exposure are a

concern. But when I look at Dr. Cooper's presentation, I noted that when he's talking about full fixation even for ACC-treated wood, and that was kind of new data, we're talking hours. So unless you're getting a new deck every other day or new play equipment, from your everyday exposure conditions, are you going to get hexavalent chromium over and over. Now if you use cleaning agents and reoxidize trivalent to hexavalent chromium, that could be a concern.

And then were there a couple of suggested uncertainty factors, and maybe these have changed -- Jonathan, I would apologize if I got this wrong -- for the specific case study of hexavalent chromium 1 was for a small study population 54 for the Nethercott study. And I just wanted to note that these were the 54 most sensitive people we could find in the United States in 1991. And we searched.

There was also a three-fold

uncertainty for using the LOAEL instead of a NOAEL. I would propose using -- if you want to use that factor. We really don't really consider it in our New Jersey evaluations. But if you want to use it, I would suggest using something like the 95 percent lower confidence limit on the 10 percent MET which is very consistent with the EPA's benchmark approach for setting reference doses.

You can skip this one. I'm going kind of long.

In conclusion for an induction-based reference dose, I kind of agree with other presenters that it really shouldn't exceed what the standardized patch test. And I thought when I made this presentation that was 4.4 ug/cm2. Perhaps it's much higher. I think that the dermatologists who are patch-testing people have the real world experience. And, you know, they aren't uncomfortable with this level of exposure, don't believe that it is causing sensitization.

It's also kind of consistent with the human maximization test data of 39 ug/cm2. If you divide by 10 for intraspecies uncertainty, you would end up with a reference dose of around 4. Similarly, I use the LLNA data of the summary data that was reported Schneider and Akkan with a EC3 value of 40 ug/cm2 dividing by 10-fold uncertainty factor for interspecies and arrived at an induction-based RFD of around 4 ug/cm2.

So I kind of see some consistency there. I don't know if it necessarily means it's right.

And then finally for an elicitation-based reference dose, I would recommend the 10 percent MET from the Nethercott 1994 study. Or if you wanted to use a more conservative measure to account for the fact that there was some reaction at that level, the lower confidence limit on that number.

Anymore questions or comments?

DR. HEERINGA: Thank you very much, Ms. Proctor.

DR. MENNE: I think it's such a pity because it's such a fine study. But how can you conclude as you do and how can Fowler do it. If you read the text on the first part of the study, you have it here on the slides, your own slide. And you actually are not mentioning so much about it. You have the Fowler results, 1991, Round 1, 16 of the 26 without any reaction. And that's all what you're telling us.

But what is Fowler telling us? Let's see here. I'm quoting, "For the remaining 10 participants, the morphology of the responses observed in Round 1 ranged from mild to severe, occasionally to extensive reticulation, occasional to many papules, mild to moderate erythema, and mild scaling. And that's after two to three days with an exposure of 25 ppm. The patch test concentration that is not irritating used in the U.S. 1,770 ppm."

So this is a nonirritating concentration and it is quite severe reactions. It was nearly half of the 26 after two days.

You know, if you had continued just a few more days, you would have severe reaction on those arms. These figures are far below the threshold. And I don't understand how they can conclude how they do it. I have discussed this with many of my colleagues in Europe, and they were shocked when they read it.

MS. PROCTOR: Understandably so. And I'm not a dermatologist, and I'm not going to discuss it.

I think that the one important

consideration here is that what we were trying to do was simulate puddle exposure scenarios and how a person would be exposed to the kind of the puddles we have in New Jersey. We generally concluded was what we had done the more severe exposure than what would be expected with kind of a unlimited reservoir for hexavalent chromium exposure. And really the very specific aim of this study was to determine something that could be used to evaluate cleanup in New Jersey.

Any more questions?

DR. HEERINGA: Any more questions from the Panel for Ms. Proctor?

MS. PROCTOR: Thank you.

DR. HEERINGA: Excuse me. One more.

DR. FOULDS: On the pH and the elicitation 10 percent MET tables you were interested in the acidic levels which sort of raised up the concentration for the 10 percent METs right up to sort of 12.5 from .57. Just on that table, you've quoted is it IPDC and IPC. I'm not quite sure what they stand for. One of them goes up to 10.4 and one of them is down at .72. In other words, it's not raised up the 10 percent.

MS. PROCTOR: I'm sorry. That's not a very clear table. Basically, in the Zelder and Rockter 1966 study of acid conditions with PDC, which was my abbreviation for potassium dichromate, they had a 10 percent MET could be calculated from those data of 12.5. And in the Zelder 1964 study with potassium dichromate in acid conditions, the 10 percent MET could be calculated at 10.4 ug/cm2.

But in the Zelder and Wackter 1966 study with potassium chromate, not potassium dichromate, the elicitation threshold was much lower. It was .72.

Granted that this isn't a crystal clear picture. But I found trend to be interesting and it kind of stood out to me and something to consider when evaluating environmental exposure.

And, unfortunately, I can't tell you the pH of the patches in the Nethercott study. To the best of my recollection, we tried to make the patches neutral pH. I even went back to the original work and could not find determination of the pH.

DR. PLEUS: On the Fowler study, you have the concentration that the arms were bathed in. What's the rationale for that concentration?

MS. PROCTOR: Well, we collected about 90 puddle samples in New Jersey. And the hexavalent chromium in our puddles is visible at about 1 ppm. So the highest concentration that we measured was 16.4 ppm. So we selected that 25 was the goal, but there were some variability in our actual measured concentrations. And we took a sample every day and analyzed it. So there was actually a range of exposure, 25 to 29. And I guess it was kind of selected to some degree at random. But the idea was to pick something that would kind of be a worse case puddle exposure.

DR. PLEUS: One question that I want to make sure I heard you say it correctly. And that was, for the participants in that study, they had one arm that was immersed in the chromium solution.

MS. PROCTOR: Yes.

DR. PLEUS: And was the other arm immersed in as a control.

MS. PROCTOR: It was immersed in sodium bicarbonate buffer solution. Also at pH 9.4.

DR. PLEUS: Okay. Thanks.

DR. HEERINGA: Thank you very much, Ms. Proctor. I appreciate the presentation.

MS. PROCTOR: I just want to mention a couple other things. As I was sitting listening to the Panel discussions, I noticed there was question about ACD from wood-treating exposures. And I think from historical data that is described in the 1975 NIASH criteria document which is available, I know, on OSHA's web site, you might want to take a look at that. Obviously, it's dated in 1975. So that's older data. And I do think they knew about ACD from hexavalent- chromium-treated wood in the processing of the wood itself, the workers treating the wood.

And then something that I didn't present here. But I did take the mass per area concentrations of total chromium from CCA-treated wood that had been wiped. And using EPA's SHEDS model and compared that to the Nethercott 10 percent MET, and the levels for cold weather and warm weather and mean and 75th percentile, were virtually all below the Nethercott 10 percent MET. I believe under cold conditions at the 75th percentile, it was just about equal or slightly exceeded the 10 percent MET. Thank you.

DR. HEERINGA: Thank you. We're at 5 minutes of 5. And I think the agenda had us going to 4:30 today. It's my preference at this point to conclude the proceedings for today and resume tomorrow morning at 8:30. And we would continue with the public comment.

We have four additional public commenters who have arranged to speak. Several of them have substantial presentations. So rather than rushing them through at a point where we're all relatively tiring, I would say, not tired. I don't want to say we're ineffective in our role at this point. But it is the end of the day.

And so I'd like to ask Paul Lewis if he has any concluding comments as the Designated Federal Official.

MR. LEWIS: Just a few remarks. I want to thank Dr. Heeringa for managing our meeting today and moving the Panel along and all the commenters along with the presentations. I want to thank the public for becoming actively engaged in our meeting.

Just a few remarks. We'll begin, again, with continuing our public comment tomorrow.

I did receive this afternoon a written comment from the Healthy Building Network and Beyond Pesticides. They're not available to make an oral comment. So I'll be making this available to the Panel and also will be entering it into the record in our docket office.

I also appreciate if the Panel can meet with us immediately after this meeting in our break room just to go over some administrative procedures and prepare for our discussion tomorrow.

Thank you, Dr. Heeringa.

DR. HEERINGA: Thank you, Paul.

And with that, I call this session

to a close for today and look forward to seeing everyone tomorrow morning at 8:30.

[The meeting was adjourned at 5:04 p.m.]

CERTIFICATE OF STENOTYPE REPORTER

I, Jane F. Hoffman Stenotype Reporter, do hereby certify that the foregoing proceedings were reported by me in stenotypy, transcribed under my direction and are a verbatim record of the proceedings had.

____
JANE F. HOFFMAN